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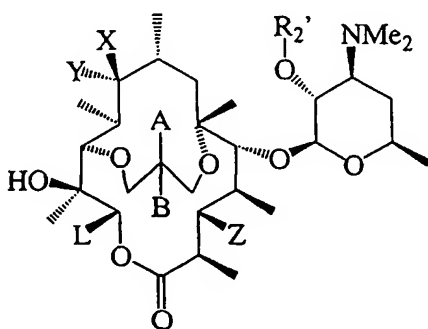
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(54) Title: 6,11 BICYCLIC ERYTHROMYCIN DERIVATIVES



(57) Abstract: The present invention discloses compounds of formula (I), or pharmaceutically acceptable salts, esters, or prodrugs thereof which exhibit antibacterial properties. The present invention further relates to pharmaceutical compositions comprising the aforementioned compounds for administration to a subject in need of antibiotic treatment. The invention also relates to methods of treating a bacterial infection in a subject by administering a pharmaceutical composition comprising the compounds of the present invention. The invention further includes process by which to make the compounds of the present invention.

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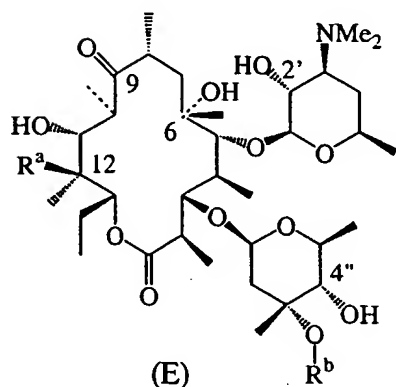
6,11 Bicyclic Erythromycin Derivatives

TECHNICAL FIELD

The present invention relates to novel semisynthetic macrolides having antibacterial activity and useful in the treatment and prevention of bacterial infections. More particularly, the invention relates to 6,11-3-carbon bridged erythromycin derivatives, compositions containing such compounds and methods for using the same, as well as processes for making such compounds.

BACKGROUND OF THE INVENTION

Erythromycins A through D, represented by formula (E) as illustrated below,



Erythromycin	R ^a	R ^b
A	-OH	-CH ₃
B	-H	-CH ₃
C	-OH	-H
D	-H	-H

are well-known and potent antibacterial agents, used widely to treat and prevent bacterial infection. As with other antibacterials, however, bacterial strains having resistance or insufficient susceptibility to erythromycin have been identified. Also, erythromycin A has only weak activity against Gram-negative bacteria. Therefore, there is a continuing need to identify new erythromycin derivative compounds which possess improved antibacterial activity, which have less potential for developing resistance, which possess the desired Gram-negative activity, or which possess unexpected selectivity against target microorganisms. Consequently, numerous investigators have prepared chemical derivatives of erythromycin in an attempt to obtain analogs having modified or improved profiles of antibiotic activity.

Kashimura *et al.* have disclosed 6-O-methylethromycin derivatives having a tricyclic basic nuclear structure in European Application 559896, published November 11,

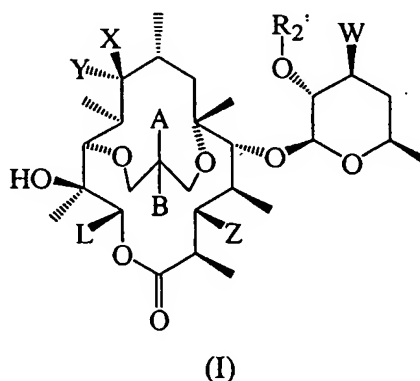
1991. Also, Asaka *et al.* have disclosed 5-O-desosminylerythronolide derivatives containing a tricyclic carbamate structure in PCT Application WO 93/21200, published April 22, 1992.

Recently erythromycin derivatives containing a variety of substituents at the 6-O position have been disclosed in U.S. patent Nos. 5,866,549, 6,075,011 and 6,420,555 B1 as well as PCT Applications WO 00/78773 and WO 03/024986. Furthermore, Ma *et. al.* have described erythromycin derivatives with aryl groups tethered to the C-6 position in *J. Med Chem.*, 44, pp 4137-4156 (2001).

SUMMARY OF THE INVENTION

The present invention provides a novel class of C6-C11 bridged erythromycin compounds that possess antibacterial activity.

In one aspect of the present invention there are disclosed novel bridged erythromycin compounds represented by formula I as illustrated below:



as well as its pharmaceutically acceptable salts, esters and prodrugs,

wherein

A is selected from:

- a) -OH;
- b) -OR_p, where R_p is a hydroxy protecting group;
- c) -R₁, where R₁ is independently selected from:

- (1) aryl;
- (2) substituted aryl;
- (3) heteroaryl; and
- (4) substituted heteroaryl;

- d) $-OR_1$, where R_1 is as previously defined;
- e) $-R_2$, where R_2 is selected from:
- (1) hydrogen;
 - (2) halogen;
 - 5 (3) C_1 - C_{12} alkyl optionally containing 0, 1, 2, or 3 heteroatoms selected from O, S or N, optionally substituted with one or more substituents selected from halogen, aryl, substituted aryl, heteroaryl, and substituted heteroaryl;
 - (4) C_2 - C_{12} alkenyl optionally containing 0, 1, 2, or 3 heteroatoms selected from O, S and N, optionally substituted with one or more substituents selected from
10 halogen, aryl, substituted aryl, heteroaryl, and substituted heteroaryl; and
 - (5) C_2 - C_{12} alkynyl optionally containing 0, 1, 2, or 3 heteroatoms selected from O, S and N, optionally substituted with one or more substituents selected from halogen, aryl, substituted aryl, heteroaryl, and substituted heteroaryl;
- f) $-OR_2$, where R_2 is independently previously defined;
- 15 g) $-S(O)_nR_{11}$, where $n = 0, 1$ or 2 , and R_{11} is independently hydrogen, R_1 or R_2 , where R_1 and R_2 are as previously defined;
- h) $-NHC(O)R_{11}$, where R_{11} is as previously defined;
- i) $-NHC(O)NHR_{11}$, where R_{11} is as previously defined;
- j) $-NHS(O)_2R_{11}$, where R_{11} is as previously defined;
- 20 k) $NR_{14}R_{15}$, where R_{14} and R_{15} are each independently R_{11} , where R_{11} is as previously defined; and
- l) $-NHR_3$, where R_3 is an amino protecting group;

B is selected from:

- a) hydrogen;
- 25 b) deuterium;
- c) halogen ;
- d) $-OH$;
- e) $-R_1$, where R_1 is as previously defined;
- f) $-R_2$, where R_2 is as previously defined; and
- 30 g) $-OR_p$, where R_p is as previously defined, provided that when B is halogen, $-OH$, or $-OR_p$, A is R_1 or R_2 ;

or alternatively, A and B taken together with the carbon atom to which they are attached are selected from:

- a) $C=O$;
- b) $C(OR_2)_2$, where R_2 is as previously defined;
- c) $C(SR_2)_2$, where R_2 is as previously defined;
- d) $C(OR_{12})(OR_{13})$, where R_{12} and R_{13} are independently C_1-C_6 alkyl or taken
 5 together are $-(CH_2)_m-$, where $m = 2$ or 3 ;
- e) $C(SR_{12})(SR_{13})$, where R_{12} , R_{13} , and m are as previously defined;
- f) $C=CHR_{11}$, where R_{11} is as previously defined;
- g) $C=N-O-R_{11}$, where R_{11} is as previously defined;
- h) $C=N-O-Ar_1-M-Ar_2$, wherein
 10 (1) $-Ar_1-$ is R_{31} , where R_{31} is independently selected from:
 - (a) $-R_1$, where R_1 is as previously defined;
 - (b) $-C_1-C_{12}$ alkyl optionally containing 0, 1, 2, or 3 heteroatoms selected from
 O, S or N, optionally substituted with one or more substituents selected
 from halogen, aryl, substituted aryl, heteroaryl, and substituted heteroaryl;
 - 15 (c) $-C_2-C_{12}$ alkenyl optionally containing 0, 1, 2, or 3 heteroatoms selected
 from O, S and N, optionally substituted with one or more substituents
 selected from halogen, aryl, substituted aryl, heteroaryl, and substituted
 heteroaryl; or
 - (d) $-C_2-C_{12}$ alkynyl optionally containing 0, 1, 2, or 3 heteroatoms selected
 20 from O, S and N, optionally substituted with one or more substituents
 selected from halogen, aryl, substituted aryl, heteroaryl, and substituted
 heteroaryl;
- (2) $-M-$ is absent or selected from:
 - (a) $-C_1-C_{12}$ alkyl optionally containing:
 - 25 1. 0-3 heteroatoms selected from O, S or N; and
 - 2. 0-3 groups selected from $-C=N-$, $-N=N-$ or $C(O)$;
 - (b) $-C_2-C_{12}$ alkenyl optionally containing:
 - 1. 0-3 heteroatoms selected from O, S or N; and
 - 2. 0-3 groups selected from $-C=N-$, $-N=N-$, or $C(O)$;
 - 30 (c) $-C_2-C_{12}$ alkynyl optionally containing:
 - 1. 0-3 heteroatoms selected from O, S or N; and
 - 2. 0-3 groups selected from $-C=N-$, $-N=N-$, or $C(O)$;
 - (d) substituted aryl;

- (e) substituted heteroaryl; or
(f) substituted heterocycloalkyl; and
(3) $-Ar_2$ is selected from:
- 5 (a) aryl;
(b) substituted aryl;
(c) heteroaryl; or
(d) substituted heteroaryl;
- i) $C=NNHR_{11}$, where R_{11} is as previously defined;
j) $C=NNHC(O)R_{11}$, where R_{11} is as previously defined;
10 k) $C=NNHC(O)NHR_{11}$, where R_{11} is as previously defined;
l) $C=NNHS(O)_2R_{11}$, where R_{11} is as previously defined;
m) $C=NNHR_3$, where R_3 is as previously defined;
n) $C=NR_{11}$, where R_{11} is as previously defined; or
o) $C=N-N=CHR_{11}$, where R_{11} is as previously defined;
- 15 one of X and Y is hydrogen and the other is selected from:
- a) hydrogen;
b) deuterium;
c) $-OH$;
d) $-OR_p$, where R_p is as previously defined;
- 20 e) $-NR_4R_5$, where R_4 and R_5 are each independently selected from:
- (1) hydrogen;
(2) C_1-C_{12} alkyl, optionally substituted with one or more substituents selected from halogen, aryl, substituted aryl, heteroaryl and substituted heteroaryl; or
(3) R_4 and R_5 , taken together with the nitrogen atom to which they are attached
25 form a 3-10 membered heteroalkyl ring containing 0-2 additional hetero atoms selected from O, S, and N; or
- alternatively, X and Y taken together with the carbon atom to which they are attached are selected from:
- a) $C=O$;
- 30 b) $C=N-Q$, wherein Q is selected from:
- (1) R_{11} , where R_{11} is as previously defined;
(2) amino protecting group;
(3) $C(O)R_{11}$, where R_{11} is as previously defined; or

(4) OR₆, where R₆ is independently selected from:

- (a) hydrogen;
 - (b) -CH₂O(CH₂)₂OCH₃;
 - (c) -CH₂O(CH₂O)_nCH₃, where n is as previously defined;
 - 5 (d) -C₁-C₁₂ alkyl, optionally substituted with one or more substituents selected from aryl, substituted aryl, heteroaryl and substituted heteroaryl;
 - (e) C₃-C₁₂ cycloalkyl;
 - (f) C(O)-C₁-C₁₂ alkyl;
 - (g) C(O)-C₃-C₁₂ cycloalkyl;
 - 10 (h) C(O)-R₁₁, where R₁₁ is as previously defined; or
 - (i) -Si(R_a)(R_b)(R_c), wherein R_a, R_b and R_c are each independently selected from C₁-C₁₂ alkyl, aryl, and substituted aryl; or
- (5) O-C(R₇)(R₈)-O-R₆, where R₆ is as previously defined, provided that R₆ is not C(O)-C₁-C₁₂ alkyl, C(O)-C₃-C₁₂ cycloalkyl, or C(O)-R₁, and R₇ and R₈ taken
- 15 together with the carbon atom to which they are attached form a C₃-C₁₂ cycloalkyl group or each independently is selected from:
- 1. hydrogen; or
 - 2. C₁-C₁₂ alkyl;

L is selected from:

- 20 b) -CH₃;
- c) -CH₂CH₃;
- d) -CH(OH)CH₃;
- e) C₁-C₆ alkyl, optionally substituted with one or more substituents selected from aryl, substituted aryl, heteroaryl, and substituted heteroaryl;
- 25 f) C₂-C₆ alkenyl, optionally substituted with one or more substituents selected from aryl, substituted aryl, heteroaryl, and substituted heteroaryl; or
- g) C₂-C₆ alkynyl, optionally substituted with one or more substituents selected from aryl, substituted aryl, heteroaryl, and substituted heteroaryl;

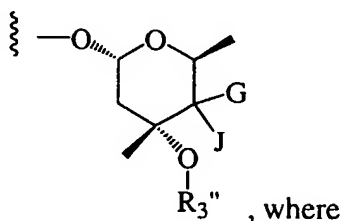
W is -NR₁₄R₁₅, where R₁₄ and R₁₅ are each independently selected from:

- 30 a) hydrogen;
- b) C₁-C₁₂ alkyl, optionally substituted with one or more substituents selected from halogen, aryl, substituted aryl, heteroaryl and substituted heteroaryl;

- c) C₂-C₁₂ alkenyl, optionally substituted with one or more substituents selected from halogen, aryl, substituted aryl, heteroaryl and substituted heteroaryl;
- d) C₂-C₁₂ alkynyl, optionally substituted with one or more substituents selected from halogen, aryl, substituted aryl, heteroaryl and substituted heteroaryl; or
- 5 e) R₁₄ and R₁₅, taken together with the nitrogen atom to which they are attached form a heterocycloalkyl cyclic moiety;

Z is selected from:

- (a) hydrogen;
- (b) -OH;
- 10 (c) -OR_p, where R_p is as previously defined;
- (d) -OR₁₁, where R₁₁ is as previously defined;
- (e) -OC(O)R₁₁, where R₁₁ is as previously defined;
- (f) -OC(O)NHR₁₁, where R₁₁ is as previously defined;
- (g) -S(O)_nR₁₁, where n and R₁₁ are as previously defined; or
- 15 (h) -



- i. R₃' is hydrogen or methyl; and
- ii. where one of J or G is hydrogen, the other is selected from:
 1. hydrogen;
 - 20 2. deuterium;
 3. -OH;
 4. -OR_p, where R_p is previously defined;
 5. -OR₄'', where R₄' is hydrogen or R_p, where R_p is as previously defined; or
 - 25 6. -NR₄R₅, where R₄ and R₅ is as previously defined; or
- iii. in the alternative, J and G are taken together with the carbon atom to which they are attached to form a group selected from:
 1. C=O;
 2. C=N-Q, wherein Q is as previously defined; and
 - 30 R₂' is hydrogen or R_p, where R_p is as previously defined.

In another embodiment of the present invention there are disclosed pharmaceutical compositions comprising a therapeutically effective amount of any compound of the present invention in combination with a pharmaceutically acceptable carrier or excipient. In yet another embodiment of the invention are methods of treating antibacterial infections in a subject with said pharmaceutical compositions. Suitable carriers and methods of formulation are also disclosed.

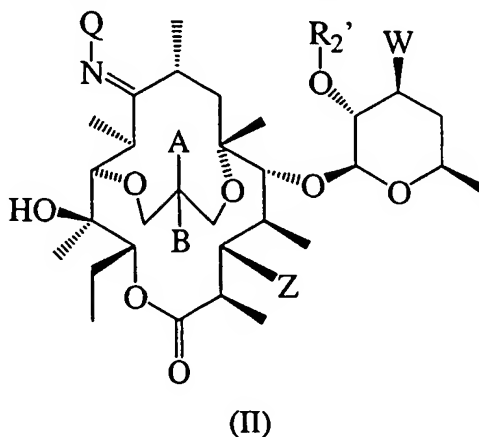
In a further aspect of the present invention there are provided processes for the preparation of 6,11-3C-bridged erythromycin derivatives of formula (I) via any synthetic route delineated herein.

DETAILED DESCRIPTION OF THE INVENTION

A first embodiment of the present invention is a compound of formula I as defined herein, or its pharmaceutically acceptable salt, ester, or prodrug.

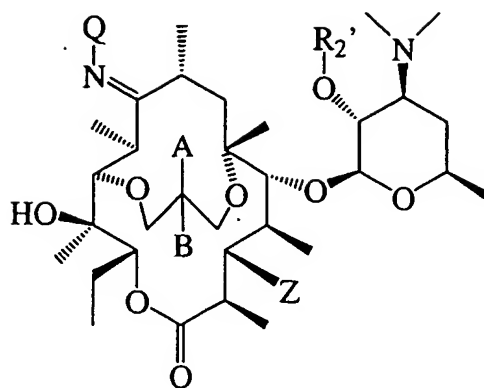
Representative subgenera of the present invention are:

A compound according to claim 1, which is represented by formula II:



where A, B, Q, R₂', W, and Z are as previously defined;

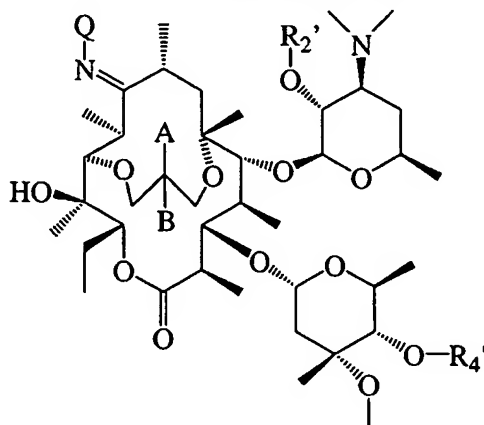
A compound according to claim 1, which is represented by formula III:



(III)

where A, B, Q, R₂', and Z are as previously defined;

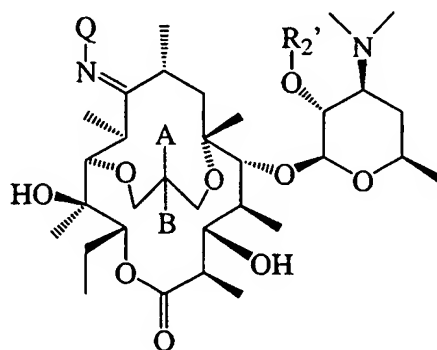
A compound according to claim 1, which is represented by formula IV:



(IV)

where A, B, Q, R₂', and R₄'' are as previously defined;

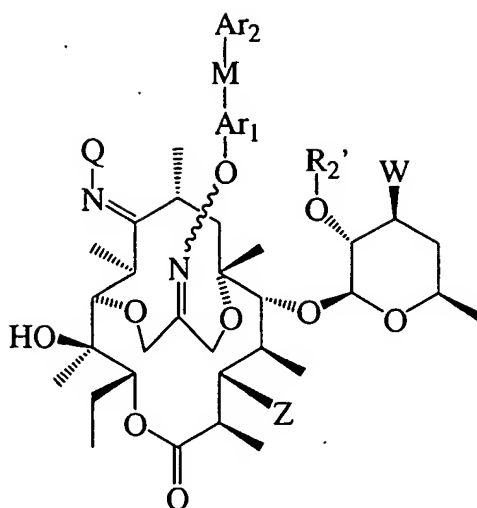
A compound according to claim 1, which is represented by formula V:



(V)

where A, B, Q, and R₂' are as previously defined;

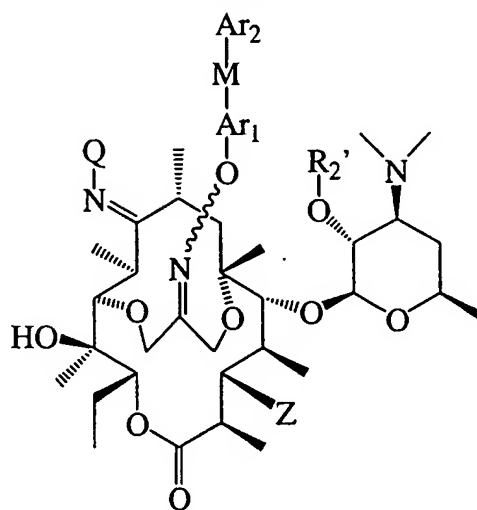
A compound according to claim 1, which is represented by formula VI:



(VI)

where Ar₁, Ar₂, M, Q, R₂', W, and Z are as previously defined;

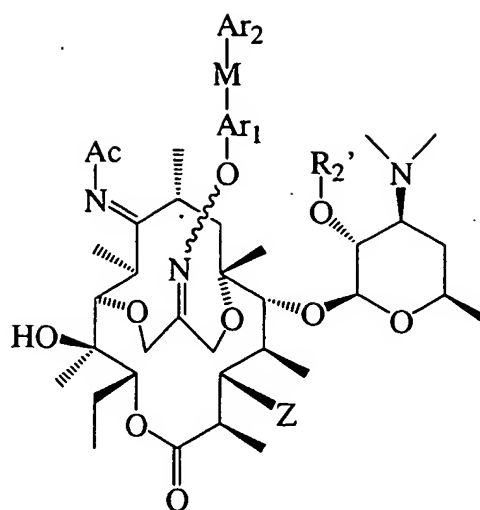
A compound according to claim 1, which is represented by formula VII:



(VII)

where Ar₁, Ar₂, M, Q, R₂', and Z are as previously defined;

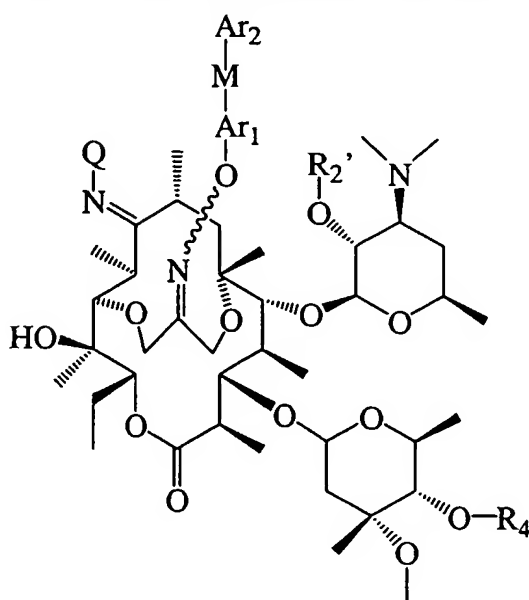
A compound according to claim 1, which is represented by formula VIII:



(VIII)

where Ar_1 , Ar_2 , M , R_2' , and Z are as previously defined;

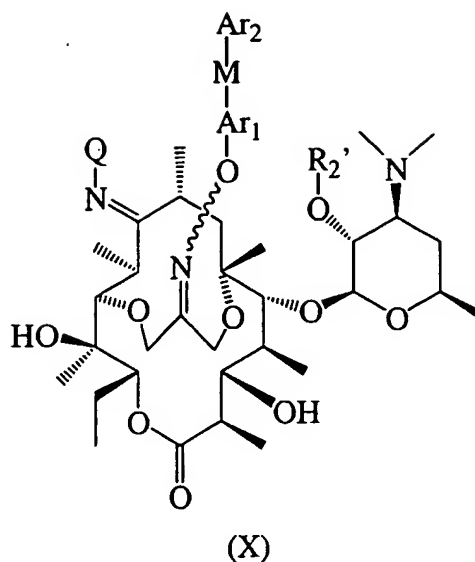
A compound according to claim 1, which is represented by formula IX:



(IX)

where Ar_1 , Ar_2 , M , Q , R_2' , and R_4 are as previously defined; and

A compound according to claim 1, which is represented by formula X:



where Ar₁, Ar₂, M, Q, and R₂' are as previously defined.

5 Representative compounds according to the invention are those selected from:

- 1) Compound of formula IV: A and B taken together with the carbon atom to which they are attached = C=CH₂, Q = OH, R₂' is H, and R₄'' = Ac;
- 2) Compound of formula IV: A and B taken together with the carbon atom to which are attached = C=CH₂, Q = H, R₂' = H, and R₄'' = Ac;
- 10 3) Compound of formula V: A and B taken together with the carbon atom to which they are attached = C=CH₂, Q = H, and R₂' = H;
- 4) Compound of formula V: A and B taken together with the carbon atom to which they are attached = C=CH₂, Q = Ac, and R₂' = H;
- 5) Compound of formula IV: A and B taken together with the carbon atom to which they are attached = C=CH₂, Q = O-CH₂OCH₃, R₂' = H, and R₄'' = Ac;
- 15 6) Compound of formula V: A and B taken together with the carbon atom to which they are attached = C=CH₂, Q = O-CH₂OCH₃, and R₂' = H;
- 7) Compound of formula I: A and B taken together with the carbon atom to which they are attached = C=CH₂, X and Y taken together with the carbon atom to which they are attached = C=NAc, L = CH₂CH₃, W is N(CH₃)₂, Z = H and R₂' = H;
- 20 8) Compound of formula I: A and B taken together with the carbon atom to which they are attached = C=CH₂, X and Y taken together with the carbon atom to which they are attached = C=NAc, L = CH₂CH₃, Z = OC(O)(p-nitrophenyl) and R₂' = H;
- 25

- 9) Compound of formula I: A and B taken together with the carbon atom to which they are attached = C=CH₂, X and Y taken together with the carbon atom to which they are attached = C=NAc, L = CH₂CH₃, W is N(CH₃)₂, Z = OC(O)[2-(NO₂), 4-(CF₃)Phenyl] and R₂' = H;
- 5 10) Compound of formula I: A and B taken together with the carbon atom to which they are attached = C=CH₂, X and Y taken together with the carbon atom to which they are attached = C=NAc, L = CH₂CH₃, W is N(CH₃)₂, Z = OC(O)CH₂(p-methoxyphenyl) and R₂' = H;
- 10 11) Compound of formula IV: A and B taken together with the carbon atom to which they are attached = C=CH₂, Q = Ac, R₂' = H, and R₄'' = Ac;
- 12) Compound of formula I: Compound of formula IV: A and B taken together with the carbon atom to which they are attached = C=O, Q = Ac, R₂' = H, and R₄'' = Ac;
- 13) Compound of formula IV: A and B taken together with the carbon atom to which they are attached = C=OBz, Q = Ac, R₂' = H, and R₄'' = Ac;
- 15 14) Compound of formula IV: A and B taken together with the carbon atom to which they are attached = C=(3-quinolyl), Q = Ac, R₂' = H, and R₄'' = Ac;
- 15) Compound of formula I: A and B taken together with the carbon atom to which they are attached = C=CH₂, X and Y taken together with the carbon atom to which they are attached = C=O, L = CH₂CH₃, W is N(CH₃)₂, Z = 4-acetoxycladinoside and R₂' = H;
- 20 16) Compound of formula I: A and B taken together with the carbon atom to which they are attached = C=CH-quinolin-3-yl, X and Y taken together with the carbon atom to which they are attached = C=O, L = CH₂CH₃, W is N(CH₃)₂, Z = 4-acetoxycladinoside and R₂' = H;
- 25 17) Compound of formula I: A and B taken together with the carbon atom to which they are attached = C=CH-quinolin-3-yl, X and Y taken together with the carbon atom to which they are attached = C=O, L = CH₂CH₃, W is N(CH₃)₂, Z = OH, and R₂' = H;
- 30 18) Compound of formula I: A and B taken together with the carbon atom to which they are attached = C=CH₂, X and Y taken together with the carbon atom to which they are attached = C=O, L = CH₂CH₃, W is N(CH₃)₂, Z = OH and R₂' = H;

- 19) Compound of formula IV: A and B taken together with the carbon atom to which they are attached = C=CH₂-phenyl, Q = OH, R₂' = H, and R₄'' = Ac;
- 20) Compound of formula V: A and B taken together with the carbon atom to which they are attached are C=CH-phenyl, Q = Ac, and R₂' = H;
- 5 21) Compound of formula I: A and B taken together with the carbon atom to which they are attached = C=O, X and Y taken together with the carbon atom to which they are attached = C=NAc, L = CH₂CH₃, W is N(CH₃)₂, Z = OCH₂CH=CH(quinolin-3-yl), and R₂' = H;
- 10 22) Compound of formula I: A and B taken together with the carbon atom to which they are attached = C=CHCHCH-phenyl, X and Y taken together with the carbon atom to which they are attached = C=NAc, L = CH₂CH₃, W is N(CH₃)₂, Z = OC(O)-benzyl and R₂' = H;
- 15 23) Compound of formula I: A and B taken together with the carbon atom to which they are attached = C=CHCHCH-phenyl, X and Y taken together with the carbon atom to which they are attached = C=NAc, L = CH₂CH₃, W is N(CH₃)₂, Z = OC(O)CH₂(2-pyridyl) and R₂' = H;
- 20 24) Compound of formula I: A and B taken together with the carbon atom to which they are attached = C=CH₂, X and Y taken together with the carbon atom to which they are attached = C=NOH, L = CH₂CH₃, W is N(CH₃)₂, Z = 4-oxocladinose and R₂' = H;
- 25 25) Compound of formula I: A and B taken together with the carbon atom to which they are attached = C=CH₂, X and Y taken together with the carbon atom to which they are attached = C=NOH, L = CH₂CH₃, W is N(CH₃)₂, Z = 4-oximecladinose and R₂' = H;
- 26) Compound of formula IV: A and B taken together with the carbon atom to which they are attached are C=CH₂, Q = OH, and R₂' = R₄'' = H;
- 27) Compound of formula I: Compound of formula IV: A and B taken together with the carbon atom to which they are attached = C=CH₂, Q = OH, R₂' = H, and R₄'' = Ac.
- 30

In another aspect, the present invention relates to a method for controlling a bacterial infection in a subject (e.g., mammal, human, horse, dog, cat, fish) comprising administering to the subject a therapeutically effective amount of a pharmaceutical composition described herein. The method includes administering to the subject (including a subject identified as in

need of such treatment) a therapeutically effective amount of any compound delineated herein, or any pharmaceutical composition delineated herein to produce such effect.

Yet another aspect of this invention relates to a method of treating a subject (e.g., mammal, human, horse, dog, cat, fish) having bacterial infection or disease or disease symptom related to having a bacterial infection (including diseases delineated herein). The method includes administering to the subject (including a subject identified as in need of such treatment) an effective amount of a compound described herein, or a composition described herein to produce such effect. Identifying a subject in need of such treatment can be in the judgment of a subject or a health care professional and can be subjective (e.g. opinion) or objective (e.g. measurable by a test or diagnostic method).

Also within the scope of this invention is a packaged product. The packaged product includes a container, one of the aforementioned compounds in the container, and a legend (e.g., a label or an insert) associated with the container and indicating administration of the compound for treating a disorder associated with bacterial infection, including the diseases delineated herein.

In a further aspect of the present invention is a process of making any compound delineated herein via any synthetic route delineated herein.

Definitions

Listed below are definitions of various terms used to describe this invention. These definitions apply to the terms as they are used throughout this specification and claims, unless otherwise limited in specific instances, either individually or as part of a larger group.

The terms "C₁-C₃ alkyl," "C₁-C₆ alkyl," or "C₁-C₁₂ alkyl," as used herein, refer to saturated, straight- or branched-chain hydrocarbon radicals containing between one and three, one and twelve, or one and six carbon atoms, respectively. Examples of C₁-C₃ alkyl radicals include methyl, ethyl, propyl and isopropyl radicals; examples of C₁-C₆ alkyl radicals include, but are not limited to, methyl, ethyl, propyl, isopropyl, *n*-butyl, *tert*-butyl, neopentyl and *n*-hexyl radicals; and examples of C₁-C₁₂ alkyl radicals include, but are not limited to, ethyl, propyl, isopropyl, *n*-hexyl, octyl, decyl, dodecyl radicals.

The term "substituted alkyl," as used herein, refers to a "C₂-C₁₂ alkyl" or "C₁-C₆ alkyl" group as previously defined, substituted by independent replacement or one, two, or three of the hydrogen atoms thereon with substituents including, but not limited to, -F, -Cl, -Br, -I, -OH, protected hydroxy, -NO₂, -CN, -C₁-C₁₂-alkyl optionally substituted with

5 halogen, C₂-C₁₂-alkenyl optionally substituted with halogen, -C₂-C₁₂-alkynyl optionally substituted with halogen, -NH₂, protected amino, -NH -C₁-C₁₂-alkyl, -NH -C₂-C₁₂-alkenyl, -NH -C₂-C₁₂-alkenyl, -NH -C₃-C₁₂-cycloalkyl, -NH -aryl, -NH -heteroaryl, -NH -heterocycloalkyl, -dialkylamino, -diarylamino, -diheteroarylamino, -O-C₁-C₁₂-alkyl, -O-C₂-C₁₂-alkenyl, -O-C₂-C₁₂-alkenyl, -O-C₃-C₁₂-cycloalkyl, -O-aryl, -O-heteroaryl, -O-

10 heterocycloalkyl, -C(O)- C₁-C₁₂-alkyl, -C(O)- C₂-C₁₂-alkenyl, -C(O)- C₂-C₁₂-alkenyl, -C(O)-C₃-C₁₂-cycloalkyl, -C(O)-aryl, -C(O)-heteroaryl, -C(O)-heterocycloalkyl, -CONH₂, -CONH- C₁-C₁₂-alkyl, -CONH- C₂-C₁₂-alkenyl, -CONH- C₂-C₁₂-alkenyl, -CONH-C₃-C₁₂-cycloalkyl, -CONH-aryl, -CONH-heteroaryl, -CONH-heterocycloalkyl, -OCO₂- C₁-C₁₂-alkyl, -OCO₂- C₂-C₁₂-alkenyl, -OCO₂- C₂-C₁₂-alkenyl, -OCO₂-C₃-C₁₂-cycloalkyl, -OCO₂-

15 aryl, -OCO₂-heteroaryl, -OCO₂-heterocycloalkyl, -OCONH₂, -OCONH- C₁-C₁₂-alkyl, -OCONH- C₂-C₁₂-alkenyl, -OCONH- C₂-C₁₂-alkenyl, -OCONH- C₃-C₁₂-cycloalkyl, -OCONH- aryl, -OCONH- heteroaryl, -OCONH- heterocycloalkyl, -NHC(O)- C₁-C₁₂-alkyl, -NHC(O)-C₂-C₁₂-alkenyl, -NHC(O)-C₂-C₁₂-alkenyl, -NHC(O)-C₃-C₁₂-cycloalkyl, -NHC(O)-aryl, -NHC(O)-heteroaryl, -NHC(O)-heterocycloalkyl, -NHCO₂- C₁-C₁₂-alkyl,

20 -NHCO₂- C₂-C₁₂-alkenyl, -NHCO₂- C₂-C₁₂-alkenyl, -NHCO₂- C₃-C₁₂-cycloalkyl, -NHCO₂- aryl, -NHCO₂- heteroaryl, -NHCO₂- heterocycloalkyl, -NHC(O)NH₂, NHC(O)NH- C₁-C₁₂-alkyl, -NHC(O)NH-C₂-C₁₂-alkenyl, -NHC(O)NH-C₂-C₁₂-alkenyl, -NHC(O)NH-C₃-C₁₂-cycloalkyl, -NHC(O)NH-aryl, -NHC(O)NH-heteroaryl, -NHC(O)NH-heterocycloalkyl, NHC(S)NH₂, NHC(S)NH- C₁-C₁₂-alkyl, -NHC(S)NH-C₂-C₁₂-alkenyl, -NHC(S)NH-C₂-C₁₂-alkenyl, -NHC(S)NH-C₃-C₁₂-cycloalkyl, -NHC(S)NH-aryl, -NHC(S)NH-heteroaryl,

25 -NHC(S)NH-heterocycloalkyl, -NHC(NH)NH₂, NHC(NH)NH- C₁-C₁₂-alkyl, -NHC(NH)NH-C₂-C₁₂-alkenyl, -NHC(NH)NH-C₂-C₁₂-alkenyl, -NHC(NH)NH-C₃-C₁₂-cycloalkyl, -NHC(NH)NH-aryl, -NHC(NH)NH-heteroaryl, -NHC(NH)NH-heterocycloalkyl, NHC(NH)-C₁-C₁₂-alkyl, -NHC(NH)-C₂-C₁₂-alkenyl, -NHC(NH)-C₂-C₁₂-alkenyl, -NHC(NH)-C₃-C₁₂-cycloalkyl, -NHC(NH)-aryl, -NHC(NH)-heteroaryl,

30 -NHC(NH)-heterocycloalkyl, -C(NH)NH-C₁-C₁₂-alkyl, -C(NH)NH-C₂-C₁₂-alkenyl, -C(NH)NH-C₂-C₁₂-alkenyl, -C(NH)NH-C₃-C₁₂-cycloalkyl, -C(NH)NH-aryl, -C(NH)NH-

heteroaryl, -C(NH)NH-heterocycloalkyl, -S(O)-C₁-C₁₂-alkyl, -S(O)-C₂-C₁₂-alkenyl, -S(O)-C₂-C₁₂-alkenyl, -S(O)-C₃-C₁₂-cycloalkyl, -S(O)-aryl, -S(O)-heteroaryl, -S(O)-heterocycloalkyl -SO₂NH₂, -SO₂NH-C₁-C₁₂-alkyl, -SO₂NH-C₂-C₁₂-alkenyl, -SO₂NH-C₂-C₁₂-alkenyl, -SO₂NH-C₃-C₁₂-cycloalkyl, -SO₂NH-aryl, -SO₂NH-heteroaryl, -SO₂NH-heterocycloalkyl, -NHSO₂-C₁-C₁₂-alkyl, -NHSO₂-C₂-C₁₂-alkenyl, -NHSO₂-C₂-C₁₂-alkenyl, -NHSO₂-C₃-C₁₂-cycloalkyl, -NHSO₂-aryl, -NHSO₂-heteroaryl, -NHSO₂-heterocycloalkyl, -CH₂NH₂, -CH₂SO₂CH₃, -aryl, -arylalkyl, -heteroaryl, -heteroarylalkyl, -heterocycloalkyl, -C₃-C₁₂-cycloalkyl, -methoxymethoxy, -methoxyethoxy, -SH, -S-C₁-C₁₂-alkyl, -S-C₂-C₁₂-alkenyl, -S-C₂-C₁₂-alkenyl, -S-C₃-C₁₂-cycloalkyl, -S-aryl, -S-heteroaryl, -S-heterocycloalkyl, or methylthiomethyl.

The terms "C₂-C₁₂ alkenyl" or "C₂-C₆ alkenyl," as used herein, denote a monovalent group derived from a hydrocarbon moiety containing from two to twelve or two to six carbon atoms having at least one carbon-carbon double bond by the removal of a single hydrogen atom. Alkenyl groups include, but are not limited to, for example, ethenyl, propenyl, butenyl, 1-methyl-2-buten-1-yl, and the like.

The term "substituted alkenyl," as used herein, refers to a "C₂-C₁₂ alkenyl" or "C₂-C₆ alkenyl" group as previously defined, substituted by independent replacement or one, two, or three of the hydrogen atoms thereon with substituents including, but not limited to, -F, -Cl, -Br, -I, -OH, protected hydroxy, -NO₂, -CN, -C₁-C₁₂-alkyl optionally substituted with halogen, C₂-C₁₂-alkenyl optionally substituted with halogen, -C₂-C₁₂-alkynyl optionally substituted with halogen, -NH₂, protected amino, -NH-C₁-C₁₂-alkyl, -NH-C₂-C₁₂-alkenyl, -NH-C₂-C₁₂-alkenyl, -NH-C₃-C₁₂-cycloalkyl, -NH-aryl, -NH-heteroaryl, -NH-heterocycloalkyl, -dialkylamino, -diarylamino, -diheteroarylamino, -O-C₁-C₁₂-alkyl, -O-C₂-C₁₂-alkenyl, -O-C₂-C₁₂-alkenyl, -O-C₃-C₁₂-cycloalkyl, -O-aryl, -O-heteroaryl, -O-heterocycloalkyl, -C(O)-C₁-C₁₂-alkyl, -C(O)-C₂-C₁₂-alkenyl, -C(O)-C₂-C₁₂-alkenyl, -C(O)-C₃-C₁₂-cycloalkyl, -C(O)-aryl, -C(O)-heteroaryl, -C(O)-heterocycloalkyl, -CONH₂, -CONH-C₁-C₁₂-alkyl, -CONH-C₂-C₁₂-alkenyl, -CONH-C₂-C₁₂-alkenyl, -CONH-C₃-C₁₂-cycloalkyl, -CONH-aryl, -CONH-heteroaryl, -CONH-heterocycloalkyl, -OCO₂-C₁-C₁₂-alkyl, -OCO₂-C₂-C₁₂-alkenyl, -OCO₂-C₂-C₁₂-alkenyl, -OCO₂-C₃-C₁₂-cycloalkyl, -OCO₂-aryl, -OCO₂-heteroaryl, -OCO₂-heterocycloalkyl, -OCONH₂, -OCONH-C₁-C₁₂-alkyl,

-OCONH- C₂-C₁₂-alkenyl, -OCONH- C₂-C₁₂-alkenyl, -OCONH- C₃-C₁₂-cycloalkyl,
 -OCONH- aryl, -OCONH- heteroaryl, -OCONH- heterocycloalkyl, -NHC(O)- C₁-C₁₂-
 alkyl, -NHC(O)-C₂-C₁₂-alkenyl, -NHC(O)-C₂-C₁₂-alkenyl, -NHC(O)-C₃-C₁₂-cycloalkyl,
 -NHC(O)-aryl, -NHC(O)-heteroaryl, -NHC(O)-heterocycloalkyl, -NHCO₂- C₁-C₁₂-alkyl,
 5 -NHCO₂- C₂-C₁₂-alkenyl, -NHCO₂- C₂-C₁₂-alkenyl, -NHCO₂- C₃-C₁₂-cycloalkyl, -NHCO₂-
 aryl, -NHCO₂- heteroaryl, -NHCO₂- heterocycloalkyl, -NHC(O)NH₂, NHC(O)NH- C₁-C₁₂-
 alkyl, -NHC(O)NH-C₂-C₁₂-alkenyl, -NHC(O)NH-C₂-C₁₂-alkenyl, -NHC(O)NH-C₃-C₁₂-
 cycloalkyl, -NHC(O)NH-aryl, -NHC(O)NH-heteroaryl, -NHC(O)NH-heterocycloalkyl,
 NHC(S)NH₂, NHC(S)NH- C₁-C₁₂-alkyl, -NHC(S)NH-C₂-C₁₂-alkenyl, -NHC(S)NH-C₂-C₁₂-
 10 alkenyl, -NHC(S)NH-C₃-C₁₂-cycloalkyl, -NHC(S)NH-aryl, -NHC(S)NH-heteroaryl,
 -NHC(S)NH-heterocycloalkyl, -NHC(NH)NH₂, NHC(NH)NH- C₁-C₁₂-alkyl,
 -NHC(NH)NH-C₂-C₁₂-alkenyl, -NHC(NH)NH-C₂-C₁₂-alkenyl, -NHC(NH)NH-C₃-C₁₂-
 cycloalkyl, -NHC(NH)NH-aryl, -NHC(NH)NH-heteroaryl, -NHC(NH)NH-
 heterocycloalkyl, NHC(NH)-C₁-C₁₂-alkyl, -NHC(NH)-C₂-C₁₂-alkenyl, -NHC(NH)-C₂-C₁₂-
 15 alkenyl, -NHC(NH)-C₃-C₁₂-cycloalkyl, -NHC(NH)-aryl, -NHC(NH)-heteroaryl,
 -NHC(NH)-heterocycloalkyl, -C(NH)NH-C₁-C₁₂-alkyl, -C(NH)NH-C₂-C₁₂-alkenyl,
 -C(NH)NH-C₂-C₁₂-alkenyl, -C(NH)NH-C₃-C₁₂-cycloalkyl, -C(NH)NH-aryl, -C(NH)NH-
 heteroaryl, -C(NH)NH-heterocycloalkyl, -S(O)-C₁-C₁₂-alkyl, - S(O)-C₂-C₁₂-alkenyl, -
 S(O)-C₂-C₁₂-alkenyl, - S(O)-C₃-C₁₂-cycloalkyl, - S(O)-aryl, - S(O)-heteroaryl, - S(O)-
 20 heterocycloalkyl -SO₂NH₂, -SO₂NH- C₁-C₁₂-alkyl, -SO₂NH- C₂-C₁₂-alkenyl, -SO₂NH- C₂-
 C₁₂-alkenyl, -SO₂NH- C₃-C₁₂-cycloalkyl, -SO₂NH- aryl, -SO₂NH- heteroaryl, -SO₂NH-
 heterocycloalkyl, -NHSO₂-C₁-C₁₂-alkyl, -NHSO₂-C₂-C₁₂-alkenyl, - NHSO₂-C₂-C₁₂-alkenyl,
 -NHSO₂-C₃-C₁₂-cycloalkyl, -NHSO₂-aryl, -NHSO₂-heteroaryl, -NHSO₂-heterocycloalkyl,
 -CH₂NH₂, -CH₂SO₂CH₃, -aryl, -arylalkyl, -heteroaryl, -heteroarylalkyl, -heterocycloalkyl,
 25 -C₃-C₁₂-cycloalkyl, -methoxymethoxy, -methoxyethoxy, -SH, -S-C₁-C₁₂-alkyl, -S-C₂-C₁₂-
 alkenyl, -S-C₂-C₁₂-alkenyl, -S-C₃-C₁₂-cycloalkyl, -S-aryl, -S-heteroaryl, -S-
 heterocycloalkyl, or methylthiomethyl.

The terms "C₂-C₁₂ alkynyl" or "C₂-C₆ alkynyl," as used herein, denote a monovalent
 30 group derived from a hydrocarbon moiety containing from two to twelve or two to six carbon
 atoms having at least one carbon-carbon triple bond by the removal of a single hydrogen

atom. Representative alkynyl groups include, but are not limited to, for example, ethynyl, 1-propynyl, 1-butynyl, and the like.

The term "substituted alkynyl," as used herein, refers to a "C₂-C₁₂ alkynyl" or "C₂-C₆ alkynyl" group as previously defined, substituted by independent replacement of one, two, or three of the hydrogen atoms thereon with substituents including, but not limited to, -F, -Cl, -Br, -I, -OH, protected hydroxy, -NO₂, -CN, -C₁-C₁₂-alkyl optionally substituted with halogen, C₂-C₁₂-alkenyl optionally substituted with halogen, -C₂-C₁₂-alkynyl optionally substituted with halogen, -NH₂, protected amino, -NH-C₁-C₁₂-alkyl, -NH-C₂-C₁₂-alkenyl, -NH-C₂-C₁₂-alkenyl, -NH-C₃-C₁₂-cycloalkyl, -NH-aryl, -NH-heteroaryl, -NH-heterocycloalkyl, -dialkylamino, -diarylamino, -diheteroarylamino, -O-C₁-C₁₂-alkyl, -O-C₂-C₁₂-alkenyl, -O-C₂-C₁₂-alkenyl, -O-C₃-C₁₂-cycloalkyl, -O-aryl, -O-heteroaryl, -O-heterocycloalkyl, -C(O)-C₁-C₁₂-alkyl, -C(O)-C₂-C₁₂-alkenyl, -C(O)-C₂-C₁₂-alkenyl, -C(O)-C₃-C₁₂-cycloalkyl, -C(O)-aryl, -C(O)-heteroaryl, -C(O)-heterocycloalkyl, -CONH₂, -CONH-C₁-C₁₂-alkyl, -CONH-C₂-C₁₂-alkenyl, -CONH-C₂-C₁₂-alkenyl, -CONH-C₃-C₁₂-cycloalkyl, -CONH-aryl, -CONH-heteroaryl, -CONH-heterocycloalkyl, -OCO₂-C₁-C₁₂-alkyl, -OCO₂-C₂-C₁₂-alkenyl, -OCO₂-C₂-C₁₂-alkenyl, -OCO₂-C₃-C₁₂-cycloalkyl, -OCO₂-aryl, -OCO₂-heteroaryl, -OCO₂-heterocycloalkyl, -OCONH₂, -OCONH-C₁-C₁₂-alkyl, -OCONH-C₂-C₁₂-alkenyl, -OCONH-C₂-C₁₂-alkenyl, -OCONH-C₃-C₁₂-cycloalkyl, -OCONH-aryl, -OCONH-heteroaryl, -OCONH-heterocycloalkyl, -NHC(O)-C₁-C₁₂-alkyl, -NHC(O)-C₂-C₁₂-alkenyl, -NHC(O)-C₂-C₁₂-alkenyl, -NHC(O)-C₃-C₁₂-cycloalkyl, -NHC(O)-aryl, -NHC(O)-heteroaryl, -NHC(O)-heterocycloalkyl, -NHCO₂-C₁-C₁₂-alkyl, -NHCO₂-C₂-C₁₂-alkenyl, -NHCO₂-C₂-C₁₂-alkenyl, -NHCO₂-C₃-C₁₂-cycloalkyl, -NHCO₂-aryl, -NHCO₂-heteroaryl, -NHCO₂-heterocycloalkyl, -NHC(O)NH₂, NHC(O)NH-C₁-C₁₂-alkyl, -NHC(O)NH-C₂-C₁₂-alkenyl, -NHC(O)NH-C₂-C₁₂-alkenyl, -NHC(O)NH-C₃-C₁₂-cycloalkyl, -NHC(O)NH-aryl, -NHC(O)NH-heteroaryl, -NHC(O)NH-heterocycloalkyl, NHC(S)NH₂, NHC(S)NH-C₁-C₁₂-alkyl, -NHC(S)NH-C₂-C₁₂-alkenyl, -NHC(S)NH-C₂-C₁₂-alkenyl, -NHC(S)NH-C₃-C₁₂-cycloalkyl, -NHC(S)NH-aryl, -NHC(S)NH-heteroaryl, -NHC(S)NH-heterocycloalkyl, -NHC(NH)NH₂, NHC(NH)NH-C₁-C₁₂-alkyl, -NHC(NH)NH-C₂-C₁₂-alkenyl, -NHC(NH)NH-C₂-C₁₂-alkenyl, -NHC(NH)NH-C₃-C₁₂-cycloalkyl, -NHC(NH)NH-aryl, -NHC(NH)NH-heteroaryl, -NHC(NH)NH-heterocycloalkyl, NHC(NH)-C₁-C₁₂-alkyl, -NHC(NH)-C₂-C₁₂-alkenyl, -NHC(NH)-C₂-C₁₂-

alkenyl, -NHC(NH)-C₃-C₁₂-cycloalkyl, -NHC(NH)-aryl, -NHC(NH)-heteroaryl,
 -NHC(NH)-heterocycloalkyl, -C(NH)NH-C₁-C₁₂-alkyl, -C(NH)NH-C₂-C₁₂-alkenyl,
 -C(NH)NH-C₂-C₁₂-alkenyl, -C(NH)NH-C₃-C₁₂-cycloalkyl, -C(NH)NH-aryl, -C(NH)NH-
 heteroaryl, -C(NH)NH-heterocycloalkyl, -S(O)-C₁-C₁₂-alkyl, -S(O)-C₂-C₁₂-alkenyl, -
 5 S(O)-C₂-C₁₂-alkenyl, -S(O)-C₃-C₁₂-cycloalkyl, -S(O)-aryl, -S(O)-heteroaryl, -S(O)-
 heterocycloalkyl -SO₂NH₂, -SO₂NH-C₁-C₁₂-alkyl, -SO₂NH-C₂-C₁₂-alkenyl, -SO₂NH-C₂-
 C₁₂-alkenyl, -SO₂NH-C₃-C₁₂-cycloalkyl, -SO₂NH-aryl, -SO₂NH-heteroaryl, -SO₂NH-
 heterocycloalkyl, -NHSO₂-C₁-C₁₂-alkyl, -NHSO₂-C₂-C₁₂-alkenyl, -NHSO₂-C₂-C₁₂-alkenyl,
 -NHSO₂-C₃-C₁₂-cycloalkyl, -NHSO₂-aryl, -NHSO₂-heteroaryl, -NHSO₂-heterocycloalkyl,
 10 -CH₂NH₂, -CH₂SO₂CH₃, -aryl, -arylalkyl, -heteroaryl, -heteroarylalkyl, -heterocycloalkyl,
 -C₃-C₁₂-cycloalkyl, -methoxymethoxy, -methoxyethoxy, -SH, -S-C₁-C₁₂-alkyl, -S-C₂-C₁₂-
 alkenyl, -S-C₂-C₁₂-alkenyl, -S-C₃-C₁₂-cycloalkyl, -S-aryl, -S-heteroaryl, -S-
 heterocycloalkyl, or methylthiomethyl.

15 The term "C₁-C₆ alkoxy," as used herein, refers to a C₁-C₆ alkyl group, as previously
 defined, attached to the parent molecular moiety through an oxygen atom. Examples of C₁-
 C₆-alkoxy include, but are not limited to, methoxy, ethoxy, propoxy, isopropoxy, *n*-butoxy,
tert-butoxy, neopentoxy and *n*-hexoxy.

20 The terms "halo" and "halogen," as used herein, refer to an atom selected from
 fluorine, chlorine, bromine and iodine.

 The term "aryl," as used herein, refers to a mono- or bicyclic carbocyclic ring system
 having one or two aromatic rings including, but not limited to, phenyl, naphthyl,
 25 tetrahydronaphthyl, indanyl, idenyl and the like.

 The term "substituted aryl," as used herein, refers to an aryl group, as previously
 defined, substituted by independent replacement or one, two, or three of the hydrogen atoms
 thereon with substituents including, but not limited to, -F, -Cl, -Br, -I, -OH, protected
 30 hydroxy, -NO₂, -CN, -C₁-C₁₂-alkyl optionally substituted with halogen, C₂-C₁₂-alkenyl
 optionally substituted with halogen, -C₂-C₁₂-alkynyl optionally substituted with halogen,
 -NH₂, protected amino, -NH-C₁-C₁₂-alkyl, -NH-C₂-C₁₂-alkenyl, -NH-C₂-C₁₂-alkenyl,

- NH-C₃-C₁₂-cycloalkyl, -NH-aryl, -NH-heteroaryl, -NH-heterocycloalkyl,
 -dialkylamino, -diarylamino, -diheteroarylamino, -O-C₁-C₁₂-alkyl, -O-C₂-C₁₂-alkenyl, -O-
 C₂-C₁₂-alkenyl, -O-C₃-C₁₂-cycloalkyl, -O-aryl, -O-heteroaryl, -O-heterocycloalkyl, -C(O)-
 C₁-C₁₂-alkyl, -C(O)-C₂-C₁₂-alkenyl, -C(O)-C₂-C₁₂-alkenyl, -C(O)-C₃-C₁₂-cycloalkyl,
 5 -C(O)-aryl, -C(O)-heteroaryl, -C(O)-heterocycloalkyl, -CONH₂, -CONH-C₁-C₁₂-alkyl,
 -CONH-C₂-C₁₂-alkenyl, -CONH-C₂-C₁₂-alkenyl, -CONH-C₃-C₁₂-cycloalkyl, -CONH-
 aryl, -CONH-heteroaryl, -CONH-heterocycloalkyl, -OCO₂-C₁-C₁₂-alkyl, -OCO₂-C₂-C₁₂-
 alkenyl, -OCO₂-C₂-C₁₂-alkenyl, -OCO₂-C₃-C₁₂-cycloalkyl, -OCO₂-aryl, -OCO₂-heteroaryl,
 -OCO₂-heterocycloalkyl, -OCONH₂, -OCONH-C₁-C₁₂-alkyl, -OCONH-C₂-C₁₂-alkenyl,
 10 -OCONH-C₂-C₁₂-alkenyl, -OCONH-C₃-C₁₂-cycloalkyl, -OCONH-aryl, -OCONH-
 heteroaryl, -OCONH-heterocycloalkyl, -NHC(O)-C₁-C₁₂-alkyl, -NHC(O)-C₂-C₁₂-alkenyl,
 -NHC(O)-C₂-C₁₂-alkenyl, -NHC(O)-C₃-C₁₂-cycloalkyl, -NHC(O)-aryl, -NHC(O)-
 heteroaryl, -NHC(O)-heterocycloalkyl, -NHCO₂-C₁-C₁₂-alkyl, -NHCO₂-C₂-C₁₂-alkenyl,
 -NHCO₂-C₂-C₁₂-alkenyl, -NHCO₂-C₃-C₁₂-cycloalkyl, -NHCO₂-aryl, -NHCO₂-
 15 heteroaryl, -NHCO₂-heterocycloalkyl, -NHC(O)NH₂, NHC(O)NH-C₁-C₁₂-alkyl,
 -NHC(O)NH-C₂-C₁₂-alkenyl, -NHC(O)NH-C₂-C₁₂-alkenyl, -NHC(O)NH-C₃-C₁₂-
 cycloalkyl, -NHC(O)NH-aryl, -NHC(O)NH-heteroaryl, -NHC(O)NH-heterocycloalkyl,
 NHC(S)NH₂, NHC(S)NH-C₁-C₁₂-alkyl, -NHC(S)NH-C₂-C₁₂-alkenyl, -NHC(S)NH-C₂-C₁₂-
 alkenyl, -NHC(S)NH-C₃-C₁₂-cycloalkyl, -NHC(S)NH-aryl, -NHC(S)NH-heteroaryl,
 20 -NHC(S)NH-heterocycloalkyl, -NHC(NH)NH₂, NHC(NH)NH-C₁-C₁₂-alkyl,
 -NHC(NH)NH-C₂-C₁₂-alkenyl, -NHC(NH)NH-C₂-C₁₂-alkenyl, -NHC(NH)NH-C₃-C₁₂-
 cycloalkyl, -NHC(NH)NH-aryl, -NHC(NH)NH-heteroaryl, -NHC(NH)NH-
 heterocycloalkyl, NHC(NH)-C₁-C₁₂-alkyl, -NHC(NH)-C₂-C₁₂-alkenyl, -NHC(NH)-C₂-C₁₂-
 alkenyl, -NHC(NH)-C₃-C₁₂-cycloalkyl, -NHC(NH)-aryl, -NHC(NH)-heteroaryl,
 25 -NHC(NH)-heterocycloalkyl, -C(NH)NH-C₁-C₁₂-alkyl, -C(NH)NH-C₂-C₁₂-alkenyl,
 -C(NH)NH-C₂-C₁₂-alkenyl, -C(NH)NH-C₃-C₁₂-cycloalkyl, -C(NH)NH-aryl, -C(NH)NH-
 heteroaryl, -C(NH)NH-heterocycloalkyl, -S(O)-C₁-C₁₂-alkyl, -S(O)-C₂-C₁₂-alkenyl, -
 S(O)-C₂-C₁₂-alkenyl, -S(O)-C₃-C₁₂-cycloalkyl, -S(O)-aryl, -S(O)-heteroaryl, -S(O)-
 heterocycloalkyl -SO₂NH₂, -SO₂NH-C₁-C₁₂-alkyl, -SO₂NH-C₂-C₁₂-alkenyl, -SO₂NH-C₂-
 30 C₁₂-alkenyl, -SO₂NH-C₃-C₁₂-cycloalkyl, -SO₂NH-aryl, -SO₂NH-heteroaryl, -SO₂NH-
 heterocycloalkyl, -NHSO₂-C₁-C₁₂-alkyl, -NHSO₂-C₂-C₁₂-alkenyl, -NHSO₂-C₂-C₁₂-alkenyl,

-NHSO₂-C₃-C₁₂-cycloalkyl, -NHSO₂-aryl, -NHSO₂-heteroaryl, -NHSO₂-heterocycloalkyl,
 -CH₂NH₂, -CH₂SO₂CH₃, -aryl, -arylalkyl, -heteroaryl, -heteroarylalkyl, -heterocycloalkyl,
 -C₃-C₁₂-cycloalkyl, -methoxymethoxy, -methoxyethoxy, -SH, -S-C₁-C₁₂-alkyl, -S-C₂-C₁₂-
 alkenyl, -S-C₂-C₁₂-alkenyl, -S-C₃-C₁₂-cycloalkyl, -S-aryl, -S-heteroaryl, -S-
 5 heterocycloalkyl, or methylthiomethyl.

The term "arylalkyl," as used herein, refers to a C₁-C₃ alkyl or C₁-C₆ alkyl residue
 attached to an aryl ring. Examples include, but are not limited to, benzyl, phenethyl and the
 like.

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The term "substituted arylalkyl," as used herein, refers to an arylalkyl group, as
 previously defined, substituted by independent replacement or one, two, or three of the
 hydrogen atoms thereon with substituents including, but not limited to, -F,
 -Cl, -Br, -I, -OH, protected hydroxy, -NO₂, -CN, -C₁-C₁₂-alkyl optionally substituted with
 15 halogen, C₂-C₁₂-alkenyl optionally substituted with halogen, -C₂-C₁₂-alkynyl optionally
 substituted with halogen, -NH₂, protected amino, -NH-C₁-C₁₂-alkyl, -NH-C₂-C₁₂-alkenyl,
 -NH-C₂-C₁₂-alkenyl, -NH-C₃-C₁₂-cycloalkyl, -NH-aryl, -NH-heteroaryl, -NH-
 heterocycloalkyl, -dialkylamino, -diarylamino, -diheteroarylamino, -O-C₁-C₁₂-alkyl, -O-
 C₂-C₁₂-alkenyl, -O-C₂-C₁₂-alkenyl, -O-C₃-C₁₂-cycloalkyl, -O-aryl, -O-heteroaryl, -O-
 20 heterocycloalkyl, -C(O)-C₁-C₁₂-alkyl, -C(O)-C₂-C₁₂-alkenyl, -C(O)-C₂-C₁₂-alkenyl,
 -C(O)-C₃-C₁₂-cycloalkyl, -C(O)-aryl, -C(O)-heteroaryl, -C(O)-heterocycloalkyl, -CONH₂,
 -CONH-C₁-C₁₂-alkyl, -CONH-C₂-C₁₂-alkenyl, -CONH-C₂-C₁₂-alkenyl, -CONH-C₃-C₁₂-
 cycloalkyl, -CONH-aryl, -CONH-heteroaryl, -CONH-heterocycloalkyl, -OCO₂-C₁-C₁₂-
 alkyl, -OCO₂-C₂-C₁₂-alkenyl, -OCO₂-C₂-C₁₂-alkenyl, -OCO₂-C₃-C₁₂-cycloalkyl, -OCO₂-
 25 aryl, -OCO₂-heteroaryl, -OCO₂-heterocycloalkyl, -OCONH₂, -OCONH-C₁-C₁₂-alkyl,
 -OCONH-C₂-C₁₂-alkenyl, -OCONH-C₂-C₁₂-alkenyl, -OCONH-C₃-C₁₂-cycloalkyl,
 -OCONH-aryl, -OCONH-heteroaryl, -OCONH-heterocycloalkyl, -NHC(O)-C₁-C₁₂-
 alkyl, -NHC(O)-C₂-C₁₂-alkenyl, -NHC(O)-C₂-C₁₂-alkenyl, -NHC(O)-C₃-C₁₂-cycloalkyl,
 -NHC(O)-aryl, -NHC(O)-heteroaryl, -NHC(O)-heterocycloalkyl, -NHCO₂-C₁-C₁₂-alkyl,
 30 -NHCO₂-C₂-C₁₂-alkenyl, -NHCO₂-C₂-C₁₂-alkenyl, -NHCO₂-C₃-C₁₂-cycloalkyl, -NHCO₂-
 aryl, -NHCO₂-heteroaryl, -NHCO₂-heterocycloalkyl, -NHC(O)NH₂, NHC(O)NH-C₁-C₁₂-
 alkyl, -NHC(O)NH-C₂-C₁₂-alkenyl, -NHC(O)NH-C₂-C₁₂-alkenyl, -NHC(O)NH-C₃-C₁₂-

cycloalkyl, -NHC(O)NH-aryl, -NHC(O)NH-heteroaryl, -NHC(O)NH-heterocycloalkyl, NHC(S)NH₂, NHC(S)NH-C₁-C₁₂-alkyl, -NHC(S)NH-C₂-C₁₂-alkenyl, -NHC(S)NH-C₂-C₁₂-alkenyl, -NHC(S)NH-C₃-C₁₂-cycloalkyl, -NHC(S)NH-aryl, -NHC(S)NH-heteroaryl, -NHC(S)NH-heterocycloalkyl, -NHC(NH)NH₂, NHC(NH)NH-C₁-C₁₂-alkyl, 5 -NHC(NH)NH-C₂-C₁₂-alkenyl, -NHC(NH)NH-C₂-C₁₂-alkenyl, -NHC(NH)NH-C₃-C₁₂-cycloalkyl, -NHC(NH)NH-aryl, -NHC(NH)NH-heteroaryl, -NHC(NH)NH-heterocycloalkyl, NHC(NH)-C₁-C₁₂-alkyl, -NHC(NH)-C₂-C₁₂-alkenyl, -NHC(NH)-C₂-C₁₂-alkenyl, -NHC(NH)-C₃-C₁₂-cycloalkyl, -NHC(NH)-aryl, -NHC(NH)-heteroaryl, -NHC(NH)-heterocycloalkyl, -C(NH)NH-C₁-C₁₂-alkyl, -C(NH)NH-C₂-C₁₂-alkenyl, 10 -C(NH)NH-C₂-C₁₂-alkenyl, -C(NH)NH-C₃-C₁₂-cycloalkyl, -C(NH)NH-aryl, -C(NH)NH-heteroaryl, -C(NH)NH-heterocycloalkyl, -S(O)-C₁-C₁₂-alkyl, -S(O)-C₂-C₁₂-alkenyl, -S(O)-C₂-C₁₂-alkenyl, -S(O)-C₃-C₁₂-cycloalkyl, -S(O)-aryl, -S(O)-heteroaryl, -S(O)-heterocycloalkyl -SO₂NH₂, -SO₂NH-C₁-C₁₂-alkyl, -SO₂NH-C₂-C₁₂-alkenyl, -SO₂NH-C₂-C₁₂-alkenyl, -SO₂NH-C₃-C₁₂-cycloalkyl, -SO₂NH-aryl, -SO₂NH-heteroaryl, -SO₂NH-heterocycloalkyl, -NHSO₂-C₁-C₁₂-alkyl, -NHSO₂-C₂-C₁₂-alkenyl, -NHSO₂-C₂-C₁₂-alkenyl, 15 -NHSO₂-C₃-C₁₂-cycloalkyl, -NHSO₂-aryl, -NHSO₂-heteroaryl, -NHSO₂-heterocycloalkyl, -CH₂NH₂, -CH₂SO₂CH₃, -aryl, -arylalkyl, -heteroaryl, -heteroarylalkyl, -heterocycloalkyl, -C₃-C₁₂-cycloalkyl, -methoxymethoxy, -methoxyethoxy, -SH, -S-C₁-C₁₂-alkyl, -S-C₂-C₁₂-alkenyl, -S-C₂-C₁₂-alkenyl, -S-C₃-C₁₂-cycloalkyl, -S-aryl, -S-heteroaryl, -S-heterocycloalkyl, or methylthiomethyl. 20

The term "heteroaryl," as used herein, refers to a mono-, bi-, or tri-cyclic aromatic radical or ring having from five to ten ring atoms of which one ring atom is selected from S, O and N; zero, one or two ring atoms are additional heteroatoms independently selected from S, O and N; and the remaining ring atoms are carbon, wherein any N or S contained within 25 the ring may be optionally oxidized. Heteroaryl includes, but is not limited to, pyridinyl, pyrazinyl, pyrimidinyl, pyrrolyl, pyrazolyl, imidazolyl, thiazolyl, oxazolyl, isooxazolyl, thiadiazolyl, oxadiazolyl, thiophenyl, furanyl, quinolinyl, isoquinolinyl, benzimidazolyl, benzooxazolyl, quinoxalinyl, and the like.

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The term "substituted heteroaryl," as used herein, refers to a heteroaryl group as previously defined, substituted by independent replacement of one, two, or three of the

hydrogen atoms thereon with substituents including, but not limited to, -F, -Cl, -Br, -I, -OH, protected hydroxy, -NO₂, -CN, -C₁-C₁₂-alkyl optionally substituted with halogen, C₂-C₁₂-alkenyl optionally substituted with halogen, -C₂-C₁₂-alkynyl optionally substituted with halogen, -NH₂, protected amino, -NH-C₁-C₁₂-alkyl, -NH-C₂-C₁₂-alkenyl, -NH-C₂-C₁₂-alkenyl, -NH-C₃-C₁₂-cycloalkyl, -NH-aryl, -NH-heteroaryl, -NH-heterocycloalkyl, -dialkylamino, -diarylamino, -diheteroarylamino, -O-C₁-C₁₂-alkyl, -O-C₂-C₁₂-alkenyl, -O-C₂-C₁₂-alkenyl, -O-C₃-C₁₂-cycloalkyl, -O-aryl, -O-heteroaryl, -O-heterocycloalkyl, -C(O)-C₁-C₁₂-alkyl, -C(O)-C₂-C₁₂-alkenyl, -C(O)-C₂-C₁₂-alkenyl, -C(O)-C₃-C₁₂-cycloalkyl, -C(O)-aryl, -C(O)-heteroaryl, -C(O)-heterocycloalkyl, -CONH₂, -CONH-C₁-C₁₂-alkyl, -CONH-C₂-C₁₂-alkenyl, -CONH-C₂-C₁₂-alkenyl, -CONH-C₃-C₁₂-cycloalkyl, -CONH-aryl, -CONH-heteroaryl, -CONH-heterocycloalkyl, -OCO₂-C₁-C₁₂-alkyl, -OCO₂-C₂-C₁₂-alkenyl, -OCO₂-C₂-C₁₂-alkenyl, -OCO₂-C₃-C₁₂-cycloalkyl, -OCO₂-aryl, -OCO₂-heteroaryl, -OCO₂-heterocycloalkyl, -OCONH₂, -OCONH-C₁-C₁₂-alkyl, -OCONH-C₂-C₁₂-alkenyl, -OCONH-C₂-C₁₂-alkenyl, -OCONH-C₃-C₁₂-cycloalkyl, -OCONH-aryl, -OCONH-heteroaryl, -OCONH-heterocycloalkyl, -NHC(O)-C₁-C₁₂-alkyl, -NHC(O)-C₂-C₁₂-alkenyl, -NHC(O)-C₂-C₁₂-alkenyl, -NHC(O)-C₃-C₁₂-cycloalkyl, -NHC(O)-aryl, -NHC(O)-heteroaryl, -NHC(O)-heterocycloalkyl, -NHCO₂-C₁-C₁₂-alkyl, -NHCO₂-C₂-C₁₂-alkenyl, -NHCO₂-C₂-C₁₂-alkenyl, -NHCO₂-C₃-C₁₂-cycloalkyl, -NHCO₂-aryl, -NHCO₂-heteroaryl, -NHCO₂-heterocycloalkyl, -NHC(O)NH₂, NHC(O)NH-C₁-C₁₂-alkyl, -NHC(O)NH-C₂-C₁₂-alkenyl, -NHC(O)NH-C₂-C₁₂-alkenyl, -NHC(O)NH-C₃-C₁₂-cycloalkyl, -NHC(O)NH-aryl, -NHC(O)NH-heteroaryl, -NHC(O)NH-heterocycloalkyl, NHC(S)NH₂, NHC(S)NH-C₁-C₁₂-alkyl, -NHC(S)NH-C₂-C₁₂-alkenyl, -NHC(S)NH-C₂-C₁₂-alkenyl, -NHC(S)NH-C₃-C₁₂-cycloalkyl, -NHC(S)NH-aryl, -NHC(S)NH-heteroaryl, -NHC(S)NH-heterocycloalkyl, -NHC(NH)NH₂, NHC(NH)NH-C₁-C₁₂-alkyl, -NHC(NH)NH-C₂-C₁₂-alkenyl, -NHC(NH)NH-C₂-C₁₂-alkenyl, -NHC(NH)NH-C₃-C₁₂-cycloalkyl, -NHC(NH)NH-aryl, -NHC(NH)NH-heteroaryl, -NHC(NH)NH-heterocycloalkyl, NHC(NH)-C₁-C₁₂-alkyl, -NHC(NH)-C₂-C₁₂-alkenyl, -NHC(NH)-C₂-C₁₂-alkenyl, -NHC(NH)-C₃-C₁₂-cycloalkyl, -NHC(NH)-aryl, -NHC(NH)-heteroaryl, -NHC(NH)-heterocycloalkyl, -C(NH)NH-C₁-C₁₂-alkyl, -C(NH)NH-C₂-C₁₂-alkenyl, -C(NH)NH-C₂-C₁₂-alkenyl, -C(NH)NH-C₃-C₁₂-cycloalkyl, -C(NH)NH-aryl, -C(NH)NH-heteroaryl, -C(NH)NH-heterocycloalkyl, -S(O)-C₁-C₁₂-alkyl, -S(O)-C₂-C₁₂-alkenyl, -

S(O)-C₂-C₁₂-alkenyl, -S(O)-C₃-C₁₂-cycloalkyl, -S(O)-aryl, -S(O)-heteroaryl, -S(O)-heterocycloalkyl -SO₂NH₂, -SO₂NH-C₁-C₁₂-alkyl, -SO₂NH-C₂-C₁₂-alkenyl, -SO₂NH-C₂-C₁₂-alkenyl, -SO₂NH-C₃-C₁₂-cycloalkyl, -SO₂NH-aryl, -SO₂NH-heteroaryl, -SO₂NH-heterocycloalkyl, -NHSO₂-C₁-C₁₂-alkyl, -NHSO₂-C₂-C₁₂-alkenyl, -NHSO₂-C₂-C₁₂-alkenyl, -NHSO₂-C₃-C₁₂-cycloalkyl, -NHSO₂-aryl, -NHSO₂-heteroaryl, -NHSO₂-heterocycloalkyl, -CH₂NH₂, -CH₂SO₂CH₃, -aryl, -arylalkyl, -heteroaryl, -heteroarylalkyl, -heterocycloalkyl, -C₃-C₁₂-cycloalkyl, -methoxymethoxy, -methoxyethoxy, -SH, -S-C₁-C₁₂-alkyl, -S-C₂-C₁₂-alkenyl, -S-C₂-C₁₂-alkenyl, -S-C₃-C₁₂-cycloalkyl, -S-aryl, -S-heteroaryl, -S-heterocycloalkyl, or methylthiomethyl.

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The term "C₃-C₁₂-cycloalkyl," as used herein, denotes a monovalent group derived from a monocyclic or bicyclic saturated carbocyclic ring compound by the removal of a single hydrogen atom. Examples include, but not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, bicyclo [2.2.1] heptyl, and bicyclo [2.2.2] octyl.

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The term "substituted C₃-C₁₂-cycloalkyl," as used herein, refers to a C₃-C₁₂-cycloalkyl group as previously defined, substituted by independent replacement or one, two, or three of the hydrogen atoms thereon with substituents including, but not limited to, -F, -Cl, -Br, -I, -OH, protected hydroxy, -NO₂, -CN, -C₁-C₁₂-alkyl optionally substituted with halogen, C₂-C₁₂-alkenyl optionally substituted with halogen, -C₂-C₁₂-alkynyl optionally substituted with halogen, -NH₂, protected amino, -NH-C₁-C₁₂-alkyl, -NH-C₂-C₁₂-alkenyl, -NH-C₂-C₁₂-alkenyl, -NH-C₃-C₁₂-cycloalkyl, -NH-aryl, -NH-heteroaryl, -NH-heterocycloalkyl, -dialkylamino, -diarylamino, -diheteroarylamino, -O-C₁-C₁₂-alkyl, -O-C₂-C₁₂-alkenyl, -O-C₂-C₁₂-alkenyl, -O-C₃-C₁₂-cycloalkyl, -O-aryl, -O-heteroaryl, -O-heterocycloalkyl, -C(O)-C₁-C₁₂-alkyl, -C(O)-C₂-C₁₂-alkenyl, -C(O)-C₂-C₁₂-alkenyl, -C(O)-C₃-C₁₂-cycloalkyl, -C(O)-aryl, -C(O)-heteroaryl, -C(O)-heterocycloalkyl, -CONH₂, -CONH-C₁-C₁₂-alkyl, -CONH-C₂-C₁₂-alkenyl, -CONH-C₂-C₁₂-alkenyl, -CONH-C₃-C₁₂-cycloalkyl, -CONH-aryl, -CONH-heteroaryl, -CONH-heterocycloalkyl, -OCO₂-C₁-C₁₂-alkyl, -OCO₂-C₂-C₁₂-alkenyl, -OCO₂-C₂-C₁₂-alkenyl, -OCO₂-C₃-C₁₂-cycloalkyl, -OCO₂-aryl, -OCO₂-heteroaryl, -OCO₂-heterocycloalkyl, -OCONH₂, -OCONH-C₁-C₁₂-alkyl, -OCONH-C₂-C₁₂-alkenyl, -OCONH-C₂-C₁₂-alkenyl, -OCONH-C₃-C₁₂-cycloalkyl, -OCONH-aryl, -OCONH-heteroaryl, -OCONH-heterocycloalkyl, -NHC(O)-C₁-C₁₂-

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- alkyl, -NHC(O)-C₂-C₁₂-alkenyl, -NHC(O)-C₂-C₁₂-alkenyl, -NHC(O)-C₃-C₁₂-cycloalkyl,
 -NHC(O)-aryl, -NHC(O)-heteroaryl, -NHC(O)-heterocycloalkyl, -NHCO₂-C₁-C₁₂-alkyl,
 -NHCO₂-C₂-C₁₂-alkenyl, -NHCO₂-C₂-C₁₂-alkenyl, -NHCO₂-C₃-C₁₂-cycloalkyl, -NHCO₂-
 aryl, -NHCO₂-heteroaryl, -NHCO₂-heterocycloalkyl, -NHC(O)NH₂, NHC(O)NH-C₁-C₁₂-
 5 alkyl, -NHC(O)NH-C₂-C₁₂-alkenyl, -NHC(O)NH-C₂-C₁₂-alkenyl, -NHC(O)NH-C₃-C₁₂-
 cycloalkyl, -NHC(O)NH-aryl, -NHC(O)NH-heteroaryl, -NHC(O)NH-heterocycloalkyl,
 NHC(S)NH₂, NHC(S)NH-C₁-C₁₂-alkyl, -NHC(S)NH-C₂-C₁₂-alkenyl, -NHC(S)NH-C₂-C₁₂-
 alkenyl, -NHC(S)NH-C₃-C₁₂-cycloalkyl, -NHC(S)NH-aryl, -NHC(S)NH-heteroaryl,
 -NHC(S)NH-heterocycloalkyl, -NHC(NH)NH₂, NHC(NH)NH-C₁-C₁₂-alkyl,
 10 -NHC(NH)NH-C₂-C₁₂-alkenyl, -NHC(NH)NH-C₂-C₁₂-alkenyl, -NHC(NH)NH-C₃-C₁₂-
 cycloalkyl, -NHC(NH)NH-aryl, -NHC(NH)NH-heteroaryl, -NHC(NH)NH-
 heterocycloalkyl, NHC(NH)-C₁-C₁₂-alkyl, -NHC(NH)-C₂-C₁₂-alkenyl, -NHC(NH)-C₂-C₁₂-
 alkenyl, -NHC(NH)-C₃-C₁₂-cycloalkyl, -NHC(NH)-aryl, -NHC(NH)-heteroaryl,
 -NHC(NH)-heterocycloalkyl, -C(NH)NH-C₁-C₁₂-alkyl, -C(NH)NH-C₂-C₁₂-alkenyl,
 15 -C(NH)NH-C₂-C₁₂-alkenyl, -C(NH)NH-C₃-C₁₂-cycloalkyl, -C(NH)NH-aryl, -C(NH)NH-
 heteroaryl, -C(NH)NH-heterocycloalkyl, -S(O)-C₁-C₁₂-alkyl, -S(O)-C₂-C₁₂-alkenyl, -
 S(O)-C₂-C₁₂-alkenyl, -S(O)-C₃-C₁₂-cycloalkyl, -S(O)-aryl, -S(O)-heteroaryl, -S(O)-
 heterocycloalkyl -SO₂NH₂, -SO₂NH-C₁-C₁₂-alkyl, -SO₂NH-C₂-C₁₂-alkenyl, -SO₂NH-C₂-
 C₁₂-alkenyl, -SO₂NH-C₃-C₁₂-cycloalkyl, -SO₂NH-aryl, -SO₂NH-heteroaryl, -SO₂NH-
 20 heterocycloalkyl, -NHSO₂-C₁-C₁₂-alkyl, -NHSO₂-C₂-C₁₂-alkenyl, -NHSO₂-C₂-C₁₂-alkenyl,
 -NHSO₂-C₃-C₁₂-cycloalkyl, -NHSO₂-aryl, -NHSO₂-heteroaryl, -NHSO₂-heterocycloalkyl,
 -CH₂NH₂, -CH₂SO₂CH₃, -aryl, -arylalkyl, -heteroaryl, -heteroarylalkyl, -heterocycloalkyl,
 -C₃-C₁₂-cycloalkyl, -methoxymethoxy, -methoxyethoxy, -SH, -S-C₁-C₁₂-alkyl, -S-C₂-C₁₂-
 alkenyl, -S-C₂-C₁₂-alkenyl, -S-C₃-C₁₂-cycloalkyl, -S-aryl, -S-heteroaryl, -S-
 25 heterocycloalkyl, or methylthiomethyl.

The term "heterocycloalkyl," as used herein, refers to a non-aromatic 5-, 6- or 7-
 membered ring or a bi- or tri-cyclic group fused system, where (i) each ring contains between
 one and three heteroatoms independently selected from oxygen, sulfur and nitrogen, (ii) each
 30 5-membered ring has 0 to 1 double bonds and each 6-membered ring has 0 to 2 double bonds,
 (iii) the nitrogen and sulfur heteroatoms may optionally be oxidized, (iv) the nitrogen
 heteroatom may optionally be quaternized, and (iv) any of the above rings may be fused to a

benzene ring. Representative heterocycloalkyl groups include, but are not limited to, [1,3]dioxolane, pyrrolidinyl, pyrazolinyl, pyrazolidinyl, imidazolinyl, imidazolidinyl, piperidinyl, piperazinyl, oxazolidinyl, isoxazolidinyl, morpholinyl, thiazolidinyl, isothiazolidinyl, and tetrahydrofuryl.

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The term "substituted heterocycloalkyl," as used herein, refers to a heterocycloalkyl group, as previously defined, substituted by independent replacement or one, two, or three of the hydrogen atoms thereon with substituents including, but not limited to, -F, -Cl, -Br, -I, -OH, protected hydroxy, -NO₂, -CN, -C₁-C₁₂-alkyl optionally substituted with halogen, C₂-C₁₂-alkenyl optionally substituted with halogen, -C₂-C₁₂-alkynyl optionally substituted with halogen, -NH₂, protected amino, -NH-C₁-C₁₂-alkyl, -NH-C₂-C₁₂-alkenyl, -NH-C₂-C₁₂-alkenyl, -NH-C₃-C₁₂-cycloalkyl, -NH-aryl, -NH-heteroaryl, -NH-heterocycloalkyl, -dialkylamino, -diarylamino, -diheteroaryl amino, -O-C₁-C₁₂-alkyl, -O-C₂-C₁₂-alkenyl, -O-C₂-C₁₂-alkenyl, -O-C₃-C₁₂-cycloalkyl, -O-aryl, -O-heteroaryl, -O-heterocycloalkyl, -C(O)-C₁-C₁₂-alkyl, -C(O)-C₂-C₁₂-alkenyl, -C(O)-C₂-C₁₂-alkenyl, -C(O)-C₃-C₁₂-cycloalkyl, -C(O)-aryl, -C(O)-heteroaryl, -C(O)-heterocycloalkyl, -CONH₂, -CONH-C₁-C₁₂-alkyl, -CONH-C₂-C₁₂-alkenyl, -CONH-C₂-C₁₂-alkenyl, -CONH-C₃-C₁₂-cycloalkyl, -CONH-aryl, -CONH-heteroaryl, -CONH-heterocycloalkyl, -OCO₂-C₁-C₁₂-alkyl, -OCO₂-C₂-C₁₂-alkenyl, -OCO₂-C₂-C₁₂-alkenyl, -OCO₂-C₃-C₁₂-cycloalkyl, -OCO₂-aryl, -OCO₂-heteroaryl, -OCO₂-heterocycloalkyl, -OCONH₂, -OCONH-C₁-C₁₂-alkyl, -OCONH-C₂-C₁₂-alkenyl, -OCONH-C₂-C₁₂-alkenyl, -OCONH-C₃-C₁₂-cycloalkyl, -OCONH-aryl, -OCONH-heteroaryl, -OCONH-heterocycloalkyl, -NHC(O)-C₁-C₁₂-alkyl, -NHC(O)-C₂-C₁₂-alkenyl, -NHC(O)-C₂-C₁₂-alkenyl, -NHC(O)-C₃-C₁₂-cycloalkyl, -NHC(O)-aryl, -NHC(O)-heteroaryl, -NHC(O)-heterocycloalkyl, -NHCO₂-C₁-C₁₂-alkyl, -NHCO₂-C₂-C₁₂-alkenyl, -NHCO₂-C₂-C₁₂-alkenyl, -NHCO₂-C₃-C₁₂-cycloalkyl, -NHCO₂-aryl, -NHCO₂-heteroaryl, -NHCO₂-heterocycloalkyl, -NHC(O)NH₂, NHC(O)NH-C₁-C₁₂-alkyl, -NHC(O)NH-C₂-C₁₂-alkenyl, -NHC(O)NH-C₂-C₁₂-alkenyl, -NHC(O)NH-C₃-C₁₂-cycloalkyl, -NHC(O)NH-aryl, -NHC(O)NH-heteroaryl, -NHC(O)NH-heterocycloalkyl, NHC(S)NH₂, NHC(S)NH-C₁-C₁₂-alkyl, -NHC(S)NH-C₂-C₁₂-alkenyl, -NHC(S)NH-C₂-C₁₂-alkenyl, -NHC(S)NH-C₃-C₁₂-cycloalkyl, -NHC(S)NH-aryl, -NHC(S)NH-heteroaryl, -NHC(S)NH-heterocycloalkyl, -NHC(NH)NH₂, NHC(NH)NH-C₁-C₁₂-alkyl, -NHC(NH)NH-C₂-C₁₂-alkenyl, -NHC(NH)NH-C₂-C₁₂-alkenyl, -NHC(NH)NH-C₃-C₁₂-

cycloalkyl, -NHC(NH)NH-aryl, -NHC(NH)NH-heteroaryl, -NHC(NH)NH-heterocycloalkyl, NHC(NH)-C₁-C₁₂-alkyl, -NHC(NH)-C₂-C₁₂-alkenyl, -NHC(NH)-C₂-C₁₂-alkenyl, -NHC(NH)-C₃-C₁₂-cycloalkyl, -NHC(NH)-aryl, -NHC(NH)-heteroaryl, -NHC(NH)-heterocycloalkyl, -C(NH)NH-C₁-C₁₂-alkyl, -C(NH)NH-C₂-C₁₂-alkenyl, -C(NH)NH-C₂-C₁₂-alkenyl, -C(NH)NH-C₃-C₁₂-cycloalkyl, -C(NH)NH-aryl, -C(NH)NH-heteroaryl, -C(NH)NH-heterocycloalkyl, -S(O)-C₁-C₁₂-alkyl, -S(O)-C₂-C₁₂-alkenyl, -S(O)-C₂-C₁₂-alkenyl, -S(O)-C₃-C₁₂-cycloalkyl, -S(O)-aryl, -S(O)-heteroaryl, -S(O)-heterocycloalkyl -SO₂NH₂, -SO₂NH-C₁-C₁₂-alkyl, -SO₂NH-C₂-C₁₂-alkenyl, -SO₂NH-C₂-C₁₂-alkenyl, -SO₂NH-C₃-C₁₂-cycloalkyl, -SO₂NH-aryl, -SO₂NH-heteroaryl, -SO₂NH-heterocycloalkyl, -NHSO₂-C₁-C₁₂-alkyl, -NHSO₂-C₂-C₁₂-alkenyl, -NHSO₂-C₂-C₁₂-alkenyl, -NHSO₂-C₃-C₁₂-cycloalkyl, -NHSO₂-aryl, -NHSO₂-heteroaryl, -NHSO₂-heterocycloalkyl, -CH₂NH₂, -CH₂SO₂CH₃, -aryl, -arylalkyl, -heteroaryl, -heteroarylalkyl, -heterocycloalkyl, -C₃-C₁₂-cycloalkyl, -methoxymethoxy, -methoxyethoxy, -SH, -S-C₁-C₁₂-alkyl, -S-C₂-C₁₂-alkenyl, -S-C₂-C₁₂-alkenyl, -S-C₃-C₁₂-cycloalkyl, -S-aryl, -S-heteroaryl, -S-heterocycloalkyl, or methylthiomethyl.

The term "heteroarylalkyl," as used herein, refers to a C₁-C₃ alkyl or C₁-C₆ alkyl residue attached to a heteroaryl ring. Examples include, but are not limited to, pyridinylmethyl, pyrimidinylethyl and the like.

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The term "substituted heteroarylalkyl," as used herein, refers to a heteroarylalkyl group, as previously defined, substituted by independent replacement or one, two, or three of the hydrogen atoms thereon with substituents including, but not limited to, -F, -Cl, -Br, -I, -OH, protected hydroxy, -NO₂, -CN, -C₁-C₁₂-alkyl optionally substituted with halogen, C₂-C₁₂-alkenyl optionally substituted with halogen, -C₂-C₁₂-alkynyl optionally substituted with halogen, -NH₂, protected amino, -NH-C₁-C₁₂-alkyl, -NH-C₂-C₁₂-alkenyl, -NH-C₂-C₁₂-alkenyl, -NH-C₃-C₁₂-cycloalkyl, -NH-aryl, -NH-heteroaryl, -NH-heterocycloalkyl, -dialkylamino, -diarylamino, -diheteroarylamino, -O-C₁-C₁₂-alkyl, -O-C₂-C₁₂-alkenyl, -O-C₂-C₁₂-alkenyl, -O-C₃-C₁₂-cycloalkyl, -O-aryl, -O-heteroaryl, -O-heterocycloalkyl, -C(O)-C₁-C₁₂-alkyl, -C(O)-C₂-C₁₂-alkenyl, -C(O)-C₂-C₁₂-alkenyl, -C(O)-C₃-C₁₂-cycloalkyl, -C(O)-aryl, -C(O)-heteroaryl, -C(O)-heterocycloalkyl, -CONH₂, -CONH-C₁-C₁₂-alkyl, -CONH-C₂-C₁₂-alkenyl, -CONH-C₂-C₁₂-alkenyl, -CONH-C₃-C₁₂-cycloalkyl, -CONH-

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- aryl, -CONH-heteroaryl, -CONH-heterocycloalkyl, -OCO₂- C₁-C₁₂-alkyl, -OCO₂- C₂-C₁₂-alkenyl, -OCO₂- C₂-C₁₂-alkenyl, -OCO₂-C₃-C₁₂-cycloalkyl, -OCO₂-aryl, -OCO₂-heteroaryl, -OCO₂-heterocycloalkyl, -OCONH₂, -OCONH- C₁-C₁₂-alkyl, -OCONH- C₂-C₁₂-alkenyl, -OCONH- C₂-C₁₂-alkenyl, -OCONH- C₃-C₁₂-cycloalkyl, -OCONH- aryl, -OCONH-
- 5 heteroaryl, -OCONH- heterocycloalkyl, -NHC(O)- C₁-C₁₂-alkyl, -NHC(O)-C₂-C₁₂-alkenyl, -NHC(O)-C₂-C₁₂-alkenyl, -NHC(O)-C₃-C₁₂-cycloalkyl, -NHC(O)-aryl, -NHC(O)-heteroaryl, -NHC(O)-heterocycloalkyl, -NHCO₂- C₁-C₁₂-alkyl, -NHCO₂- C₂-C₁₂-alkenyl, -NHCO₂- C₂-C₁₂-alkenyl, -NHCO₂- C₃-C₁₂-cycloalkyl, -NHCO₂- aryl, -NHCO₂-heteroaryl, -NHCO₂- heterocycloalkyl, -NHC(O)NH₂, NHC(O)NH- C₁-C₁₂-alkyl,
- 10 -NHC(O)NH-C₂-C₁₂-alkenyl, -NHC(O)NH-C₂-C₁₂-alkenyl, -NHC(O)NH-C₃-C₁₂-cycloalkyl, -NHC(O)NH-aryl, -NHC(O)NH-heteroaryl, -NHC(O)NH-heterocycloalkyl, NHC(S)NH₂, NHC(S)NH- C₁-C₁₂-alkyl, -NHC(S)NH-C₂-C₁₂-alkenyl, -NHC(S)NH-C₂-C₁₂-alkenyl, -NHC(S)NH-C₃-C₁₂-cycloalkyl, -NHC(S)NH-aryl, -NHC(S)NH-heteroaryl, -NHC(S)NH-heterocycloalkyl, -NHC(NH)NH₂, NHC(NH)NH- C₁-C₁₂-alkyl,
- 15 -NHC(NH)NH-C₂-C₁₂-alkenyl, -NHC(NH)NH-C₂-C₁₂-alkenyl, -NHC(NH)NH-C₃-C₁₂-cycloalkyl, -NHC(NH)NH-aryl, -NHC(NH)NH-heteroaryl, -NHC(NH)NH-heterocycloalkyl, NHC(NH)-C₁-C₁₂-alkyl, -NHC(NH)-C₂-C₁₂-alkenyl, -NHC(NH)-C₂-C₁₂-alkenyl, -NHC(NH)-C₃-C₁₂-cycloalkyl, -NHC(NH)-aryl, -NHC(NH)-heteroaryl, -NHC(NH)-heterocycloalkyl, -C(NH)NH-C₁-C₁₂-alkyl, -C(NH)NH-C₂-C₁₂-alkenyl,
- 20 -C(NH)NH-C₂-C₁₂-alkenyl, -C(NH)NH-C₃-C₁₂-cycloalkyl, -C(NH)NH-aryl, -C(NH)NH-heteroaryl, -C(NH)NH-heterocycloalkyl, -S(O)-C₁-C₁₂-alkyl, -S(O)-C₂-C₁₂-alkenyl, -S(O)-C₂-C₁₂-alkenyl, -S(O)-C₃-C₁₂-cycloalkyl, -S(O)-aryl, -S(O)-heteroaryl, -S(O)-heterocycloalkyl -SO₂NH₂, -SO₂NH- C₁-C₁₂-alkyl, -SO₂NH- C₂-C₁₂-alkenyl, -SO₂NH- C₂-C₁₂-alkenyl, -SO₂NH- C₃-C₁₂-cycloalkyl, -SO₂NH- aryl, -SO₂NH- heteroaryl, -SO₂NH-
- 25 heterocycloalkyl, -NHSO₂-C₁-C₁₂-alkyl, -NHSO₂-C₂-C₁₂-alkenyl, -NHSO₂-C₂-C₁₂-alkenyl, -NHSO₂-C₃-C₁₂-cycloalkyl, -NHSO₂-aryl, -NHSO₂-heteroaryl, -NHSO₂-heterocycloalkyl, -CH₂NH₂, -CH₂SO₂CH₃, -aryl, -arylalkyl, -heteroaryl, -heteroarylalkyl, -heterocycloalkyl, -C₃-C₁₂-cycloalkyl, -methoxymethoxy, -methoxyethoxy, -SH, -S-C₁-C₁₂-alkyl, -S-C₂-C₁₂-alkenyl, -S-C₂-C₁₂-alkenyl, -S-C₃-C₁₂-cycloalkyl, -S-aryl, -S-heteroaryl, -S-
- 30 heterocycloalkyl, or methylthiomethyl.

The term "C₁-C₆ alkoxy," as used herein, refers to a C₁-C₆ alkyl group, as previously defined, attached to the parent molecular moiety through an oxygen atom. Examples of C₁-C₆-alkoxy include, but are not limited to, methoxy, ethoxy, propoxy, isopropoxy, *n*-butoxy, *tert*-butoxy, neopentoxy and *n*-hexoxy.

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The term "C₁-C₃-alkyl-amino," as used herein, refers to one or two C₁-C₃-alkyl groups, as previously defined, attached to the parent molecular moiety through a nitrogen atom. Examples of C₁-C₃-alkyl-amino include, but are not limited to, methylamino, dimethylamino, ethylamino, diethylamino, and propylamino.

10

The term "alkylamino" refers to a group having the structure -NH(C₁-C₁₂ alkyl) where C₁-C₁₂ alkyl is as previously defined.

The term "dialkylamino" refers to a group having the structure -N(C₁-C₁₂ alkyl) (C₁-C₁₂ alkyl), where C₁-C₁₂ alkyl is as previously defined. Examples of dialkylamino are, but not limited to, dimethylamino, diethylamino, methylethylamino, piperidino, and the like.

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The term "alkoxycarbonyl" represents an ester group, i.e., an alkoxy group, attached to the parent molecular moiety through a carbonyl group such as methoxycarbonyl, ethoxycarbonyl, and the like.

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The term "carboxaldehyde," as used herein, refers to a group of formula -CHO.

The term "carboxy," as used herein, refers to a group of formula -COOH.

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The term "carboxamide," as used herein, refers to a group of formula -C(O)NH(C₁-C₁₂ alkyl) or -C(O)N(C₁-C₁₂ alkyl) (C₁-C₁₂ alkyl), -C(O)NH₂, and the like.

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The term "hydroxy protecting group," as used herein, refers to a labile chemical moiety which is known in the art to protect a hydroxyl group against undesired reactions during synthetic procedures. After said synthetic procedure(s) the hydroxy protecting group as described herein may be selectively removed. Hydroxy protecting groups as known in the art are described generally in T.H. Greene and P.G. M. Wuts, Protective Groups in Organic

Synthesis, 3rd edition, John Wiley & Sons, New York (1999). Examples of hydroxy protecting groups include, but are not limited to, methylthiomethyl, *tert*-butyl-dimethylsilyl, *tert*-butyldiphenylsilyl, acyl substituted with an aromatic group and the like.

- 5 The term "protected hydroxy," as used herein, refers to a hydroxy group protected with a hydroxy protecting group, as defined above, including benzoyl, acetyl, trimethylsilyl, triethylsilyl, methoxymethyl groups, for example.

- 10 The term "amino protecting group," as used herein, refers to a labile chemical moiety which is known in the art to protect an amino group against undesired reactions during synthetic procedures. After said synthetic procedure(s) the amino protecting group as described herein may be selectively removed. Amino protecting groups as known in the art are described generally in T.H. Greene and P.G. M. Wuts, Protective Groups in Organic
15 Synthesis, 3rd edition, John Wiley & Sons, New York (1999). Examples of amino protecting groups include, but are not limited to, *t*-butoxycarbonyl, 9-fluorenylmethoxycarbonyl, benzyloxycarbonyl, and the like.

 The term "protected amino," as used herein, refers to an amino group protected with an amino protecting group as defined above.

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- The term "aprotic solvent," as used herein, refers to a solvent that is relatively inert to proton activity, i.e., not acting as a proton-donor. Examples include, but are not limited to, hydrocarbons, such as hexane and toluene, for example, halogenated hydrocarbons, such as, for example, methylene chloride, ethylene chloride, chloroform, and the like, heterocyclic
25 compounds, such as, for example, tetrahydrofuran and *N*-methylpyrrolidinone, and ethers such as diethyl ether, bis-methoxymethyl ether. Such compounds are well known to those skilled in the art, and it will be obvious to those skilled in the art that individual solvents or mixtures thereof may be preferred for specific compounds and reaction conditions, depending upon such factors as the solubility of reagents, reactivity of reagents and preferred
30 temperature ranges, for example. Further discussions of aprotic solvents may be found in organic chemistry textbooks or in specialized monographs, for example: Organic Solvents
Physical Properties and Methods of Purification, 4th ed., edited by John A. Riddick *et al.*, Vol. II, in the Techniques of Chemistry Series, John Wiley & Sons, NY, 1986.

The term "protogenic organic solvent," as used herein, refers to a solvent that tends to provide protons, such as an alcohol, for example, methanol, ethanol, propanol, isopropanol, butanol, t-butanol, and the like. Such solvents are well known to those skilled in the art, and it will be obvious to those skilled in the art that individual solvents or mixtures thereof may be preferred for specific compounds and reaction conditions, depending upon such factors as the solubility of reagents, reactivity of reagents and preferred temperature ranges, for example. Further discussions of protogenic solvents may be found in organic chemistry textbooks or in specialized monographs, for example: Organic Solvents Physical Properties and Methods of Purification, 4th ed., edited by John A. Riddick *et al.*, Vol. II, in the Techniques of Chemistry Series, John Wiley & Sons, NY, 1986.

"An effective amount," as used herein, refers to an amount of a compound which confers a therapeutic effect on the treated subject. The therapeutic effect may be objective (i.e., measurable by some test or marker) or subjective (i.e., subject gives an indication of or feels an effect). An effective amount of the compound described above may range from about 0.1 mg/Kg to about 500 mg/Kg, preferably from about 1 to about 50 mg/Kg. Effective doses will also vary depending on route of administration, as well as the possibility of co-usage with other agents.

Combinations of substituents and variables envisioned by this invention are only those that result in the formation of stable compounds. The term "stable", as used herein, refers to compounds which possess stability sufficient to allow manufacture and which maintains the integrity of the compound for a sufficient period of time to be useful for the purposes detailed herein (e.g., therapeutic or prophylactic administration to a subject).

The synthesized compounds can be separated from a reaction mixture and further purified by a method such as column chromatography, high pressure liquid chromatography, or recrystallization. As can be appreciated by the skilled artisan, further methods of synthesizing the compounds of the formulae herein will be evident to those of ordinary skill in the art. Additionally, the various synthetic steps may be performed in an alternate sequence or order to give the desired compounds. Synthetic chemistry transformations and protecting group methodologies (protection and deprotection) useful in synthesizing the compounds described herein are known in the art and include, for example, those such as described in R. Larock, Comprehensive Organic Transformations, VCH Publishers (1989);

T.W. Greene and P.G.M. Wuts, Protective Groups in Organic Synthesis, 2d. Ed., John Wiley and Sons (1991); L. Fieser and M. Fieser, Fieser and Fieser's Reagents for Organic Synthesis, John Wiley and Sons (1994); and L. Paquette, ed., Encyclopedia of Reagents for Organic Synthesis, John Wiley and Sons (1995), and subsequent editions thereof.

5

The term "subject" as used herein refers to an animal. Preferably the animal is a mammal. More preferably the mammal is a human. A subject also refers to, for example, dogs, cats, horses, cows, pigs, guinea pigs, fish, birds and the like.

10

The compounds of this invention may be modified by appending appropriate functionalities to enhance selective biological properties. Such modifications are known in the art and may include those which increase biological penetration into a given biological system (e.g., blood, lymphatic system, central nervous system), increase oral availability, increase solubility to allow administration by injection, alter metabolism and alter rate of excretion.

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The compounds described herein contain one or more asymmetric centers and thus give rise to enantiomers, diastereomers, and other stereoisomeric forms that may be defined, in terms of absolute stereochemistry, as (R)- or (S)-, or as (D)- or (L)- for amino acids. The present invention is meant to include all such possible isomers, as well as their racemic and optically pure forms. Optical isomers may be prepared from their respective optically active precursors by the procedures described above, or by resolving the racemic mixtures. The resolution can be carried out in the presence of a resolving agent, by chromatography or by repeated crystallization or by some combination of these techniques which are known to those skilled in the art. Further details regarding resolutions can be found in Jacques, et al., Enantiomers, Racemates, and Resolutions (John Wiley & Sons, 1981). When the compounds described herein contain olefinic double bonds, other unsaturation, or other centers of geometric asymmetry, and unless specified otherwise, it is intended that the compounds include both E and Z geometric isomers or cis- and trans- isomers. Likewise, all tautomeric forms are also intended to be included. The configuration of any carbon-carbon double bond appearing herein is selected for convenience only and is not intended to designate a particular configuration unless the text so states; thus a carbon-carbon double bond or carbon-heteroatom double bond depicted arbitrarily herein as *trans* may be *cis*, *trans*, or a mixture of the two in any proportion.

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As used herein, the term "pharmaceutically acceptable salt" refers to those salts which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response and the like, and are commensurate with a reasonable benefit/risk ratio. Pharmaceutically acceptable salts are well known in the art. For example, S. M. Berge, *et al.* describes pharmaceutically acceptable salts in detail in J. Pharmaceutical Sciences, 66: 1-19 (1977). The salts can be prepared *in situ* during the final isolation and purification of the compounds of the invention, or separately by reacting the free base function with a suitable organic acid. Examples of pharmaceutically acceptable include, but are not limited to, nontoxic acid addition salts are salts of an amino group formed with inorganic acids such as hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid and perchloric acid or with organic acids such as acetic acid, maleic acid, tartaric acid, citric acid, succinic acid or malonic acid or by using other methods used in the art such as ion exchange. Other pharmaceutically acceptable salts include, but are not limited to, adipate, alginate, ascorbate, aspartate, benzenesulfonate, benzoate, bisulfate, borate, butyrate, camphorate, camphorsulfonate, citrate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, formate, fumarate, glucoheptonate, glycerophosphate, gluconate, hemisulfate, heptanoate, hexanoate, hydroiodide, 2-hydroxy-ethanesulfonate, lactobionate, lactate, laurate, lauryl sulfate, malate, maleate, malonate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, oleate, oxalate, palmitate, pamoate, pectinate, persulfate, 3-phenylpropionate, phosphate, picrate, pivalate, propionate, stearate, succinate, sulfate, tartrate, thiocyanate, *p*-toluenesulfonate, undecanoate, valerate salts, and the like. Representative alkali or alkaline earth metal salts include sodium, lithium, potassium, calcium, magnesium, and the like. Further pharmaceutically acceptable salts include, when appropriate, nontoxic ammonium, quaternary ammonium, and amine cations formed using counterions such as halide, hydroxide, carboxylate, sulfate, phosphate, nitrate, alkyl having from 1 to 6 carbon atoms, sulfonate and aryl sulfonate.

As used herein, the compounds of this invention, including the compounds of formulae described herein, are defined to include pharmaceutically acceptable derivatives or prodrugs thereof. A "pharmaceutically acceptable derivative or prodrug" means any pharmaceutically acceptable salt, ester, salt of an ester, or other derivative of a compound of

this invention which, upon administration to a recipient, is capable of providing (directly or indirectly) a compound of this invention.

When the compositions of this invention comprise a combination of a compound of
5 the formulae described herein and one or more additional therapeutic or prophylactic agents, both the compound and the additional agent should be present at dosage levels of between about 1 to 100%, and more preferably between about 5 to 95% of the dosage normally administered in a monotherapy regimen. The additional agents may be administered separately, as part of a multiple dose regimen, from the compounds of this invention.
10 Alternatively, those agents may be part of a single dosage form, mixed together with the compounds of this invention in a single composition.

As used herein, unless otherwise indicated, the term "bacterial infection(s)" or "protozoa infections"; includes, but is not limited to, bacterial infections and protozoa
15 infections that occur in mammals, fish and birds as well as disorders related to bacterial infections and protozoa infections that may be treated or prevented by administering antibiotics such as the compounds of the present invention. Such bacterial infections and protozoa infections and disorders related to such infections include, but are not limited to, the following: pneumonia, otitis media, sinusitis, bronchitis, tonsillitis, and mastoiditis related to
20 infection by *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis*, *Staphylococcus aureus*, or *Peptostreptococcus* spp. *Pseudomonas* spp.; pharyngitis, rheumatic fever, and glomerulonephritis related to infection by *Streptococcus pyogenes*, Groups C and G streptococci, *Clostridium diphtheriae*, or *Actinobacillus haemolyticum*; respiratory tract infections related to infection by *Mycoplasma pneumoniae*, *Legionella*
25 *pneumophila*, *Streptococcus pneumoniae*, *Haemophilus influenzae*, or *Chlamydia pneumoniae*; uncomplicated skin and soft tissue infections, abscesses and osteomyelitis, and puerperal fever related to infection by *Staphylococcus aureus*, coagulase-positive staphylococci (i.e., *S. epidermidis*, *S. hemolyticus*, etc.), *S. pyogenes*, *S. agalactiae*, Streptococcal groups C-F (minute-colony streptococci), viridans streptococci,
30 *Corynebacterium* spp., *Clostridium* spp., or *Bartonella henselae*; uncomplicated acute urinary tract infections related to infection by *S. saprophyticus* or *Enterococcus* spp.; urethritis and cervicitis; and sexually transmitted diseases related to infection by *Chlamydia trachomatis*, *Haemophilus ducreyi*, *Treponema pallidum*, *Ureaplasma urealyticum*, or *Nisseria gonorrhoeae*; toxin diseases related to infection by *S. aureus* (food poisoning and Toxic shock

syndrome), or Groups A, S. and C streptococci; ulcers related to infection by *Helicobacter pylori*; systemic febrile syndromes related to infection by *Borrelia recurrentis*; Lyme disease related to infection by *Borrelia burgdorferi*; conjunctivitis, keratitis, and dacrocystitis related to infection by *C. trachomatis*, *N. gonorrhoeae*, *S. aureus*, *S. pneumoniae*, *S. pyogenes*, *H.*
 5 *influenzae*, or *Listeria* spp.; disseminated *Mycobacterium avium* complex (MAC) disease related to infection by *Mycobacterium avium*, or *Mycobacterium intracellulare*; gastroenteritis related to infection by *Campylobacter jejuni*; intestinal protozoa related to infection by *Cryptosporidium* spp. odontogenic infection related to infection by viridans streptococci; persistent cough related to infection by *Bordetella pertussis*; gas gangrene
 10 related to infection by *Clostridium perfringens* or *Bacteroides* spp.; Skin infection by *S. aureus*, *Propionibacterium acne*; atherosclerosis related to infection by *Helicobacter pylori* or *Chlamydia pneumoniae*; or the like.

Bacterial infections and protozoa infections and disorders related to such infections
 15 that may be treated or prevented in animals include, but are not limited to, the following: bovine respiratory disease related to infection by *P. haemolytica.*, *P. multocida*, *Mycoplasma bovis*, or *Bordetella* spp.; cow enteric disease related to infection by *E. coli* or protozoa (i.e., coccidia, cryptosporidia, etc.), dairy cow mastitis related to infection by *S. aureus*, *S. uberis*, *S. agalactiae*, *S. dysgalactiae*, *Klebsiella* spp., *Corynebacterium*, or *Enterococcus* spp.; swine
 20 respiratory disease related to infection by *A. pleuropneumoniae.*, *P. multocida*, or *Mycoplasma* spp.; swine enteric disease related to infection by *E. coli*, *Lawsonia intracellularis*, *Salmonella* spp., or *Serpulina hyodysenteriae*; cow footrot related to infection by *Fusobacterium* spp.; cow metritis related to infection by *E. coli*; cow hairy warts related to Infection by *Fusobacterium necrophorum* or *Bacteroides nodosus*; cow pink-eye related to
 25 infection by *Moraxella bovis*, cow premature abortion related to infection by protozoa (i.e. neosporium); urinary tract infection in dogs and cats related to infection by *E. coli*; skin and soft tissue infections in dogs and cats related to infection by *S. epidermidis*, *S. intermedius*, coagulase neg. *Staphylococcus* or *P. multocida*; and dental or mouth infections in dogs and
 30 oats related to infection by *Alcaligenes* spp., *Bacteroides* spp., *Clostridium* spp., *Enterobacter* spp., *Eubacterium* spp., *Peptostreptococcus* spp., *Porphyromonas* spp., *Campylobacter* spp., *Actinomyces* spp., *Erysipelothrix* spp., *Rhodococcus* spp., *Trypanosoma* spp., *Plasmodium* spp., *Babesia* spp., *Toxoplasma* spp., *Pneumocystis* spp., *Leishmania* spp., and *Trichomonas* spp. or *Prevotella* spp. Other bacterial infections and protozoa infections and disorders related to such infections that may be treated or prevented in accord with the method of the present

invention are referred to in J. P. Sanford et al., "The Sanford Guide To Antimicrobial Therapy," 26th Edition, (Antimicrobial Therapy, Inc., 1996).

Antibacterial Activity

5 Susceptibility tests can be used to quantitatively measure the *in vitro* activity of an antimicrobial agent against a given bacterial isolate. Compounds were tested for *in vitro* antibacterial activity by a micro-dilution method. Minimal Inhibitory Concentration (MIC) was determined in 96 well microtiter plates utilizing the appropriate Mueller Hinton Broth medium (CAMHB) for the observed bacterial isolates. Antimicrobial agents were serially
10 diluted (2-fold) in DMSO to produce a concentration range from about 64 µg/ml to about 0.03 µg/ml. The diluted compounds (2 µl/well) were then transferred into sterile, uninoculated CAMHB (0.2 mL) by use of a 96 fixed tip-pipetting station. The inoculum for each bacterial strain was standardized to 5×10^5 CFU/mL by optical comparison to a 0.5 McFarland turbidity standard. The plates were inoculated with 10 µl/well of adjusted
15 bacterial inoculum. The 96 well plates were covered and incubated at $35 \pm 2^\circ\text{C}$ for 24 hours in ambient air environment. Following incubation, plate wells were visually examined by Optical Density measurement for the presence of growth (turbidity). The lowest concentration of an antimicrobial agent at which no visible growth occurs was defined as the MIC. The compounds of the invention generally demonstrated an MIC in the range from
20 about 64 µg/ml to about 0.03 µg/ml.

All *in vitro* testing follows the guidelines described in the Approved Standards M7-A4 protocol, published by the National Committee for Clinical Laboratory Standards (NCCLS).

25

Pharmaceutical Compositions.

The pharmaceutical compositions of the present invention comprise a therapeutically effective amount of a compound of the present invention formulated together with one or more pharmaceutically acceptable carriers or excipients.

30

As used herein, the term "pharmaceutically acceptable carrier or excipient" means a non-toxic, inert solid, semi-solid or liquid filler, diluent, encapsulating material or formulation auxiliary of any type. Some examples of materials which can serve as

pharmaceutically acceptable carriers are sugars such as lactose, glucose and sucrose; starches such as corn starch and potato starch; cellulose and its derivatives such as sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate; powdered tragacanth; malt; gelatin; talc; excipients such as cocoa butter and suppository waxes; oils such as peanut oil, cottonseed oil, safflower oil, sesame oil, olive oil, corn oil and soybean oil; glycols such as propylene glycol; esters such as ethyl oleate and ethyl laurate; agar; buffering agents such as magnesium hydroxide and aluminum hydroxide; alginic acid; pyrogen-free water; isotonic saline; Ringer's solution; ethyl alcohol, and phosphate buffer solutions, as well as other non-toxic compatible lubricants such as sodium lauryl sulfate and magnesium stearate, as well as coloring agents, releasing agents, coating agents, sweetening, flavoring and perfuming agents, preservatives and antioxidants can also be present in the composition, according to the judgment of the formulator.

The pharmaceutical compositions of this invention may be administered orally, parenterally, by inhalation spray, topically, rectally, nasally, buccally, vaginally or via an implanted reservoir, preferably by oral administration or administration by injection. The pharmaceutical compositions of this invention may contain any conventional non-toxic pharmaceutically-acceptable carriers, adjuvants or vehicles. In some cases, the pH of the formulation may be adjusted with pharmaceutically acceptable acids, bases or buffers to enhance the stability of the formulated compound or its delivery form. The term parenteral as used herein includes subcutaneous, intracutaneous, intravenous, intramuscular, intraarticular, intraarterial, intrasynovial, intrasternal, intrathecal, intralesional and intracranial injection or infusion techniques.

Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, microemulsions, solutions, suspensions, syrups and elixirs. In addition to the active compounds, the liquid dosage forms may contain inert diluents commonly used in the art such as, for example, water or other solvents, solubilizing agents and emulsifiers such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, dimethylformamide, oils (in particular, cottonseed, groundnut, corn, germ, olive, castor, and sesame oils), glycerol, tetrahydrofurfuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, and mixtures thereof. Besides inert diluents, the oral compositions can also include adjuvants

such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, and perfuming agents.

Injectable preparations, for example, sterile injectable aqueous or oleaginous
5 suspensions, may be formulated according to the known art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution, suspension or emulsion in a nontoxic parenterally acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution, U.S.P. and isotonic sodium
10 chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil can be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid are used in the preparation of injectables.

15 The injectable formulations can be sterilized, for example, by filtration through a bacterial-retaining filter, or by incorporating sterilizing agents in the form of sterile solid compositions which can be dissolved or dispersed in sterile water or other sterile injectable medium prior to use.

20 In order to prolong the effect of a drug, it is often desirable to slow the absorption of the drug from subcutaneous or intramuscular injection. This may be accomplished by the use of a liquid suspension of crystalline or amorphous material with poor water solubility. The rate of absorption of the drug then depends upon its rate of dissolution, which, in turn, may depend upon crystal size and crystalline form. Alternatively, delayed absorption of a
25 parenterally administered drug form is accomplished by dissolving or suspending the drug in an oil vehicle. Injectable depot forms are made by forming microencapsule matrices of the drug in biodegradable polymers such as polylactide-polyglycolide. Depending upon the ratio of drug to polymer and the nature of the particular polymer employed, the rate of drug release can be controlled. Examples of other biodegradable polymers include poly(orthoesters) and
30 poly(anhydrides). Depot injectable formulations are also prepared by entrapping the drug in liposomes or microemulsions that are compatible with body tissues.

Compositions for rectal or vaginal administration are preferably suppositories which can be prepared by mixing the compounds of this invention with suitable non-irritating

excipients or carriers such as cocoa butter, polyethylene glycol or a suppository wax which are solid at ambient temperature but liquid at body temperature and therefore melt in the rectum or vaginal cavity and release the active compound.

5 Solid dosage forms for oral administration include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active compound is mixed with at least one inert, pharmaceutically acceptable excipient or carrier such as sodium citrate or dicalcium phosphate and/or: a) fillers or extenders such as starches, lactose, sucrose, glucose, mannitol, and silicic acid, b) binders such as, for example, carboxymethylcellulose, alginates, gelatin,
10 polyvinylpyrrolidinone, sucrose, and acacia, c) humectants such as glycerol, d) disintegrating agents such as agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, and sodium carbonate, e) solution retarding agents such as paraffin, f) absorption accelerators such as quaternary ammonium compounds, g) wetting agents such as, for example, cetyl alcohol and glycerol monostearate, h) absorbents such as kaolin and bentonite
15 clay, and i) lubricants such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof. In the case of capsules, tablets and pills, the dosage form may also comprise buffering agents.

 Solid compositions of a similar type may also be employed as fillers in soft and hard-
20 filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycols and the like.

 The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings and other coatings well known in
25 the pharmaceutical formulating art. They may optionally contain opacifying agents and can also be of a composition that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract, optionally, in a delayed manner. Examples of embedding compositions that can be used include polymeric substances and waxes.

30 Dosage forms for topical or transdermal administration of a compound of this invention include ointments, pastes, creams, lotions, gels, powders, solutions, sprays, inhalants or patches. The active component is admixed under sterile conditions with a pharmaceutically acceptable carrier and any needed preservatives or buffers as may be

required. Ophthalmic formulation, ear drops, eye ointments, powders and solutions are also contemplated as being within the scope of this invention.

5 The ointments, pastes, creams and gels may contain, in addition to an active compound of this invention, excipients such as animal and vegetable fats, oils, waxes, paraffins, starch, tragacanth, cellulose derivatives, polyethylene glycols, silicones, bentonites, silicic acid, talc and zinc oxide, or mixtures thereof.

10 Powders and sprays can contain, in addition to the compounds of this invention, excipients such as lactose, talc, silicic acid, aluminum hydroxide, calcium silicates and polyamide powder, or mixtures of these substances. Sprays can additionally contain customary propellants such as chlorofluorohydrocarbons.

15 Transdermal patches have the added advantage of providing controlled delivery of a compound to the body. Such dosage forms can be made by dissolving or dispensing the compound in the proper medium. Absorption enhancers can also be used to increase the flux of the compound across the skin. The rate can be controlled by either providing a rate controlling membrane or by dispersing the compound in a polymer matrix or gel.

20 According to the methods of treatment of the present invention, bacterial infections are treated or prevented in a patient such as a human or other animals by administering to the patient a therapeutically effective amount of a compound of the invention, in such amounts and for such time as is necessary to achieve the desired result.

25 By a "therapeutically effective amount" of a compound of the invention is meant a sufficient amount of the compound to treat bacterial infections, at a reasonable benefit/risk ratio applicable to any medical treatment. It will be understood, however, that the total daily usage of the compounds and compositions of the present invention will be decided by the attending physician within the scope of sound medical judgment. The specific therapeutically
30 effective dose level for any particular patient will depend upon a variety of factors including the disorder being treated and the severity of the disorder; the activity of the specific compound employed; the specific composition employed; the age, body weight, general health, sex and diet of the patient; the time of administration, route of administration, and rate of excretion of the specific compound employed; the duration of the treatment; drugs used in

combination or contemporaneously with the specific compound employed; and like factors well known in the medical arts.

The total daily dose of the compounds of this invention administered to a human or
5 other animal in single or in divided doses can be in amounts, for example, from 0.01 to 50
mg/kg body weight or more usually from 0.1 to 25 mg/kg body weight. Single dose
compositions may contain such amounts or submultiples thereof to make up the daily dose.
In general, treatment regimens according to the present invention comprise administration to
a patient in need of such treatment from about 10 mg to about 1000 mg of the compound(s)
10 of this invention per day in single or multiple doses.

The compounds of the formulae described herein can, for example, be administered
by injection, intravenously, intraarterially, subdermally, intraperitoneally, intramuscularly, or
subcutaneously; or orally, buccally, nasally, transmucosally, topically, in an ophthalmic
15 preparation, or by inhalation, with a dosage ranging from about 0.5 to about 100 mg/kg of
body weight, alternatively dosages between 1 mg and 1000 mg/dose, every 4 to 120 hours,
or according to the requirements of the particular drug. The methods herein contemplate
administration of an effective amount of compound or compound composition to achieve the
desired or stated effect. Typically, the pharmaceutical compositions of this invention will be
20 administered from about 1 to about 6 times per day or alternatively, as a continuous infusion.
Such administration can be used as a chronic or acute therapy. The amount of active
ingredient that may be combined with the carrier materials to produce a single dosage form
will vary depending upon the host treated and the particular mode of administration. A
typical preparation will contain from about 5% to about 95% active compound (w/w).
25 Alternatively, such preparations may contain from about 20% to about 80% active
compound.

Lower or higher doses than those recited above may be required. Specific dosage and
treatment regimens for any particular patient will depend upon a variety of factors, including
30 the activity of the specific compound employed, the age, body weight, general health status,
sex, diet, time of administration, rate of excretion, drug combination, the severity and course
of the disease, condition or symptoms, the patient's disposition to the disease, condition or
symptoms, and the judgment of the treating physician.

Upon improvement of a patient's condition, a maintenance dose of a compound, composition or combination of this invention may be administered, if necessary. Subsequently, the dosage or frequency of administration, or both, may be reduced, as a function of the symptoms, to a level at which the improved condition is retained when the symptoms have been alleviated to the desired level. Patients may, however, require intermittent treatment on a long-term basis upon any recurrence of disease symptoms.

The pharmaceutical compositions of this invention can be administered orally to fish by blending said pharmaceutical compositions into fish feed or said pharmaceutical compositions may be dissolved in water in which infected fish are placed, a method commonly referred to as a medicated bath. The dosage for the treatment of fish differs depending upon the purpose of administration (prevention or cure of disease) and type of administration, size and extent of infection of the fish to be treated. Generally, a dosage of 5 - 1000 mg, preferably 20 - 100 mg, per kg of body weight of fish may be administered per day, either at one time or divided into several times. It will be recognized that the above-specified dosage is only a general range which may be reduced or increased depending upon the age, body weight, condition of disease, etc. of the fish.

Unless otherwise defined, all technical and scientific terms used herein are accorded the meaning commonly known to one with ordinary skill in the art. All publications, patents, published patent applications, and other references mentioned herein are hereby incorporated by reference in their entirety.

Abbreviations

Abbreviations which have been used in the descriptions of the scheme and the examples that follow are:

Ac for acetyl;

AIBN for azobisisobutyronitrile;

Bu₃SnH for tributyltin hydride;

CDI for carbonyldiimidazole;

dba for dibenzylidene acetone;

dppb for diphenylphosphino butane;

DBU for 1,8-diazabicyclo[5.4.0]undec-7-ene;

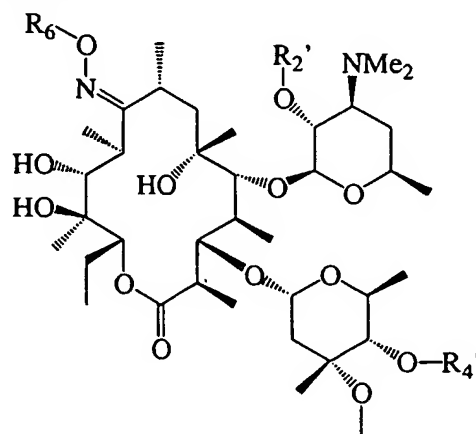
DEAD for diethylazodicarboxylate;

- DMAP for dimethylaminopyridine;
 DMF for dimethyl formamide;
 DPPA for diphenylphosphoryl azide;
 EtOAc for ethyl acetate;
 5 MeOH for methanol;
 NaN(TMS)₂ for sodium bis(trimethylsilyl)amide;
 NMMO for N-methylmorpholine N-oxide;
 TEA for triethylamine;
 THF for tetrahydrofuran;
 10 TPP or PPh₃ for triphenylphosphine;
 MOM for methoxymethyl;
 Boc for *t* - butoxycarbonyl;
 Bz for benzyl;
 Ph for phenyl;
 15 POPd for dihydrogen dichlorobis(di-*tert*-butylphosphinito-κP)palladate(II);
 TBS for *tert*-butyl dimethylsilyl; or
 TMS for trimethylsilyl.

Synthetic Methods

- 20 The compounds and processes of the present invention will be better understood in connection with the following synthetic schemes that illustrate the methods by which the compounds of the invention may be prepared.

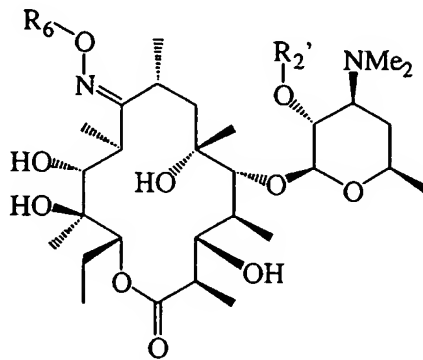
A preferred intermediate for the preparation of compounds represented by formula I is a compound represented by the formula



(XI)

where R_6 , R_2' and R_4'' are as previously defined.

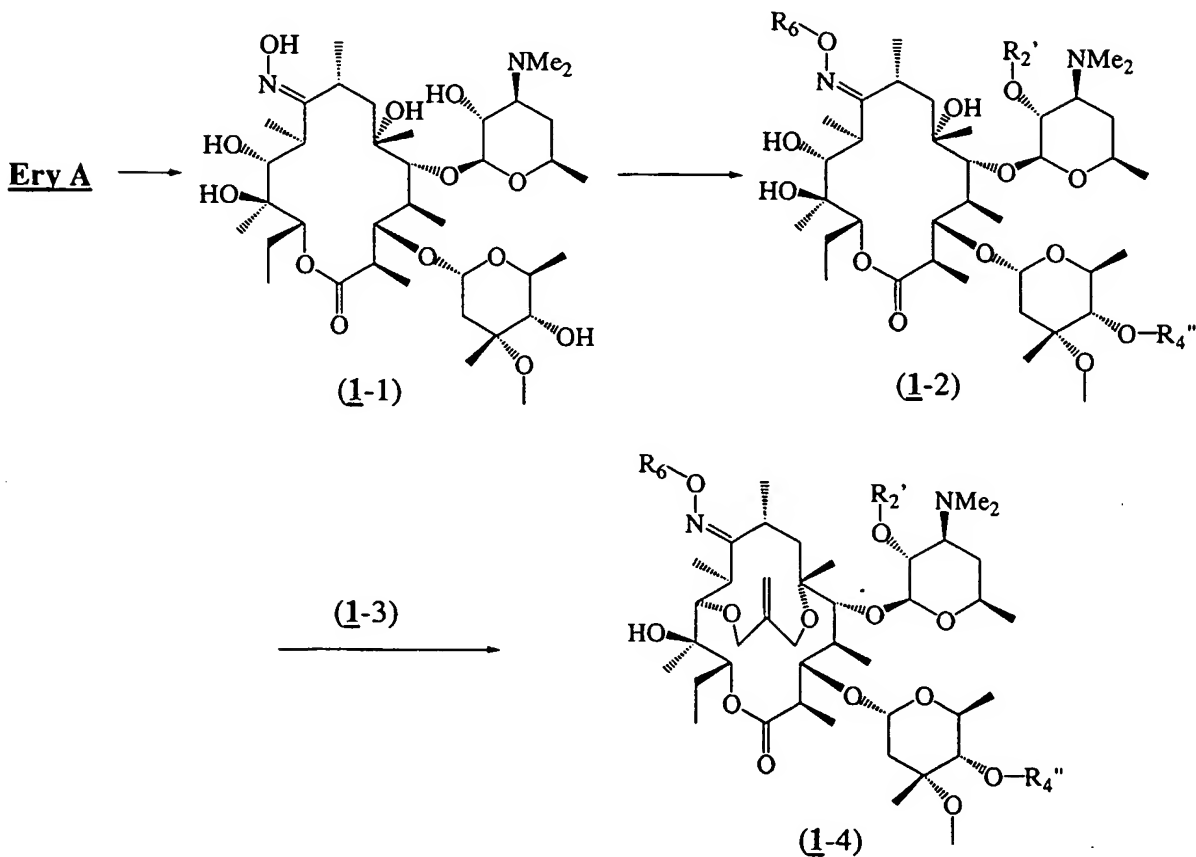
A second preferred intermediate for the preparation of compounds represented by formula I is a compound represented by the formula



(XII)

where R_6 and R_2' are as previously defined.

Scheme 1



10

A process of the invention, as illustrated in Scheme 1, involves preparing a compound of formula I (1-4) by reacting a compound of formula (1-2) with a suitable alkylating agent.

In accordance with Scheme 1, the 9-keto group of erythromycins can be initially converted into an oxime by methods described in U.S. Patent 4,990,602, followed by the

protection of the 2' - and 4''-hydroxyl and, if desired, the oxime groups of the erythromycin derivatives to obtain the compounds of formula (1-2).

The preparation of protected erythromycins is also described in U.S. Patents 4,990,602; 4,331,803; 4,680,386; 4,670,549; or European Patent Application EP 260,938.

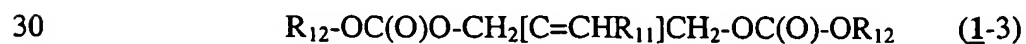
5 The 2' - and 4''-hydroxyl groups are protected by reaction with suitable hydroxyl protecting agents in an aprotic solvent. Typical hydroxyl protecting reagents include, but are not limited to, acetylating agents, silylating agents, acid anhydrides, and the like. Examples of hydroxyl protecting reagents include, but are not limited to, acetyl chloride, acetic anhydride, benzoyl chloride, benzoic anhydride, benzyl chloroformate, hexamethyldisilazane, and trialkylsilyl chlorides.

10 Examples of aprotic solvents include, but are not limited to, dichloromethane, chloroform, tetrahydrofuran, N-methylpyrrolidinone, dimethylsulfoxide, N,N-dimethylformamide, N,N -dimethylacetamide, hexamethylphosphoric triamide, a mixture thereof or a mixture of one of these solvents with ether, tetrahydrofuran, 1,2-dimethoxyethane, 1,2-dichloroethane, acetonitrile, ethyl acetate, acetone and the like. Aprotic solvents do not adversely affect the reaction. Preferably, the solvent is selected from dichloromethane, chloroform, N,N -dimethylformamide, tetrahydrofuran, N-methylpyrrolidinone or mixtures thereof. A more thorough discussion of solvents and conditions for protecting the hydroxyl group can be found in T.W. Greene and P.G.M. Wuts, 15 "Protective Groups in Organic Synthesis" 3rd ed., John Wiley & Son, Inc, 1999.

20 Protection of 2' - and 4''-hydroxyl groups may be accomplished sequentially or simultaneously to provide compound (1-2) where R₂' and/or R₄'' can be, for example, acetyl, benzoyl, trimethylsilyl, and the like. Preferred protecting groups include acetyl, benzoyl, and trimethylsilyl. A particularly preferred group for protecting the hydroxyl and oxime groups is the acetyl protecting group, wherein R₂' = R₄'' = R₆ = Ac.

25 Acetylation of the hydroxyl group is typically accomplished by treating the compound (1-1) with an acetylating reagent, for example, acetic anhydride or acetyl chloride.

 The erythromycin derivative of formula (1-1) is then reacted with an alkylating agent of the formula:



where R₁₂ is C₁-C₁₂-alkyl and R₁₁ is as previously defined.

 Most palladium (0) catalysts are expected to work in this process. Some palladium (II) catalysts, such as palladium (II) acetate, which is converted into a palladium (0) species *in-situ* by the actions of a phosphine, will work as well. See, for example, Beller et al. *Angew.*

Chem. Int. Ed. Engl., 1995, 34 (17), 1848. The palladium catalyst can be selected from, but not limited to, the group consisting of palladium (II) acetate,

tetrakis(triphenylphosphine)palladium (0), tris(dibenzylideneacetone)dipalladium, tetradibenzylideneacetone)dipalladium and the like. Palladium on carbon and palladium (II)

5 halide catalysts are less preferred than other palladium catalysts for this process.

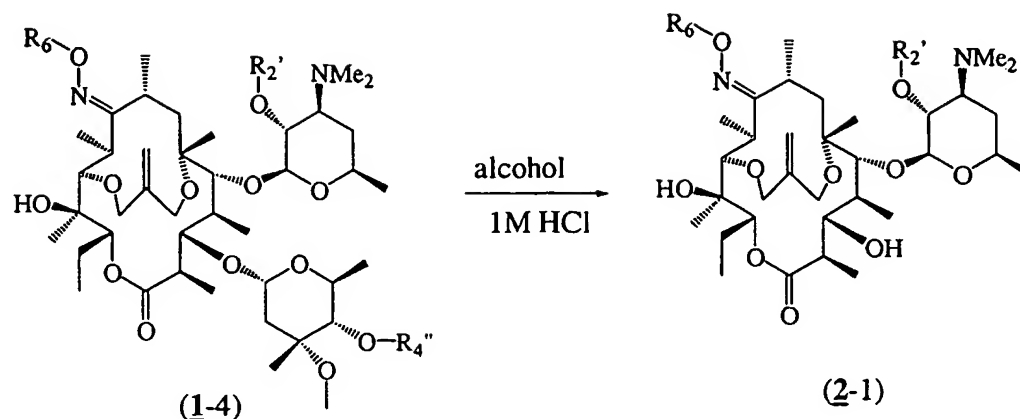
Suitable phosphines include, but are not limited to, triphenylphosphine, bis(diphenylphosphino)methane, bis(diphenylphosphino)ethane, bis(diphenylphosphino)propane, 1,4-bis(diphenylphosphino)butane, bis(diphenylphosphino)pentane, and tri-*o*-tolyl-phosphine, and the like.

10 The reaction is carried out in an aprotic solvent, preferably at elevated temperature, preferably at or above 50 °C. Suitable aprotic solvents include, but are not limited to, tetrahydrofuran, N, N-dimethylformamide, dimethyl sulfoxide, N-methyl-2-pyrrolidone, hexamethylphosphoric triamide, 1,2-dimethoxyethane, methyl-*tert*-butyl ether, heptane, acetonitrile, isopropyl acetate and ethyl acetate. The most preferred solvents are
15 tetrahydrofuran or toluene.

Generally, the alkylating agents have the formula (1-3), previously described. The preferred alkylating agents are those wherein R₁₂ is *tert*-butyl, isopropyl or isobutyl. The alkylating reagents are prepared by reaction of a diol with a wide variety of compounds for incorporating the di-carbonate moiety. The compounds include, but are not limited to, *tert*-
20 butyl chloroformate, di-*tert*-butyl dicarbonate, and 1-(*tert*-butoxycarbonyl)imidazole and the reaction is carried out in the presence of an organic or an inorganic base. The temperature of the reaction varies from about -30 °C to about 30 °C. Preferably the alkylating reagent is di-*tert*-butyl dicarbonate.

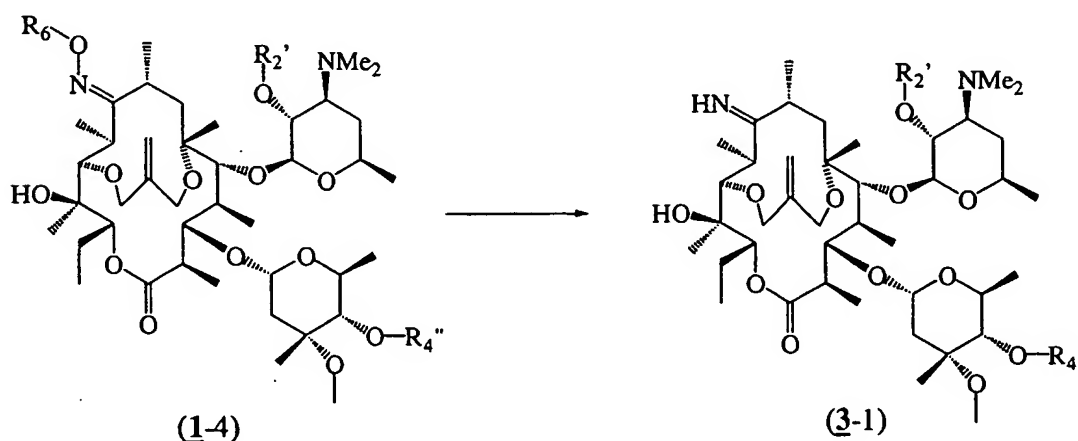
An alternative method of converting the alcohol into the carbonate involves treating
25 the alcohol with phosgene or triphosgene to prepare the chloroformate derivative of the diol. The di-chloroformate derivative is then converted into the di-carbonate by the methods described in Cotarca, L., Delogu, P., Nardelli, A., Sunijic, V, *Synthesis*, 1996, 553. The reaction can be carried out in a variety of organic solvents such as dichloromethane, toluene, diethyl ether, ethyl acetate and chloroform in the presence of a base. Examples of suitable
30 bases include, but are not limited to, sodium hydroxide, potassium hydroxide, ammonium hydroxide, sodium carbonate, potassium carbonate, ammonium carbonate, (4-dimethylamino)pyridine, pyridine, triethylamine and the like. The temperature can vary from 0 °C to about 60 °C. The reaction typically takes about 3 to 5 hours to run to completion.

Scheme 2



- Another process of the invention involves the removal of the cladinose moiety of the compounds of formula I. The cladinose moiety of the macrolide compound (1-4) is removed either by mild acid hydrolysis or by enzymatic hydrolysis to give compounds of formula (2-1) in Scheme 2. Representative acids include dilute hydrochloric acid, sulfuric acid, perchloric acid, chloroacetic acid, dichloroacetic acid or trifluoroacetic acid. Suitable solvents for the reaction include methanol, ethanol, isopropanol, butanol, water and mixtures thereof. Reaction times are typically 0.5 to 24 hours. The reaction temperature is preferably 0 to 80 °C.

Scheme 3



- Compounds of formula (1-4) where R₆ is Ac can be converted into the corresponding imine as outlined in Scheme 3. Selective deprotection of the oxime is typically accomplished via alkaline hydrolysis in protic solvents. Representative alkali include lithium hydroxide, sodium hydroxide, potassium hydroxide, and the like. Solvents which are applicable include, but are not limited to, tetrahydrofuran, 1,4-dioxane, 1,2-dimethoxyethane, isopropanol,

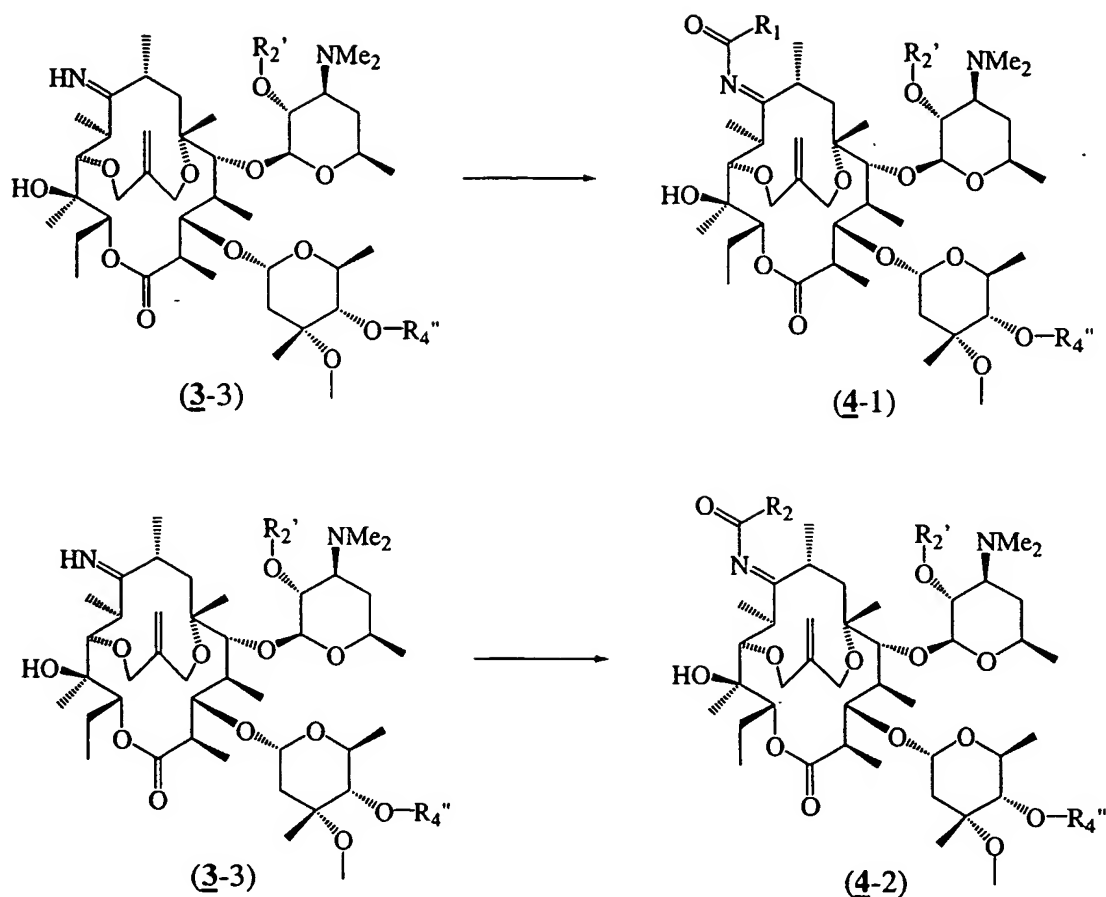
ethanol, butanol, water and mixtures thereof. The reaction temperature is preferably 0° to 35° C and reaction time is preferably 0.5 to 24 hours.

In a like fashion, simultaneous deprotection of both the oxime and the 2' hydroxyl can be accomplished under a variety of conditions. Conditions for deprotection include, but are not limited to, treating with an alcoholic solvent at from room temperature to reflux, or treatment with a primary amine, such as butylamine. Alcoholic solvents preferred for the deprotection are methanol and ethanol. A more thorough discussion of the procedures, reagents and conditions for removing protecting groups is described in the literature, for example, by T.W. Greene and P.G.M. Wuts in "Protective Groups in Organic Synthesis" 3rd ed., John Wiley & Son, Inc, 1999.

Deoxygenation of compounds of formula (1-4) where R₆ is H under reducing conditions gives the macrolide imine of formula (3-1). Many reducing agents can be used to effect this transformation including, but not limited to: lithium aluminum hydride, titanium trichloride, sodium cyanoborohydride, borane, and various sulfides such as sodium hydrogen sulfide, sodium ethoxide. For a more detailed account of oxime reduction see J. March in "Advanced Organic Chemistry" 4th ed., Wiley & Son, Inc, 1992, which is incorporated by reference herein.

A particularly useful method for the reduction of oximes to the corresponding imine uses a sulfite reducing agent, such as sodium hydrogensulfite or titanium trichloride under acidic conditions, typically in protic solvents. Representative acids include, but are not limited to, acetic acid, formic acid, dilute hydrochloric acid, dilute phosphoric acid, dilute sulfuric acid, and the like. Protic solvents include, but are not limited to, mixtures of water and methanol, ethanol, isopropanol, or butanol. The reaction is typically carried out at 25° to 110° C, preferably for between 1 and 10 hours.

Scheme 4



Another process of the invention, as illustrated in Scheme 4, involves a procedure for the acylation of imines of the formula (3-3). The imine is acylated under basic conditions using a suitable acylating agent in an aprotic solvent. Typical acylating agents include, but are not limited to, acid chlorides, acid anhydrides, and chloroformates.

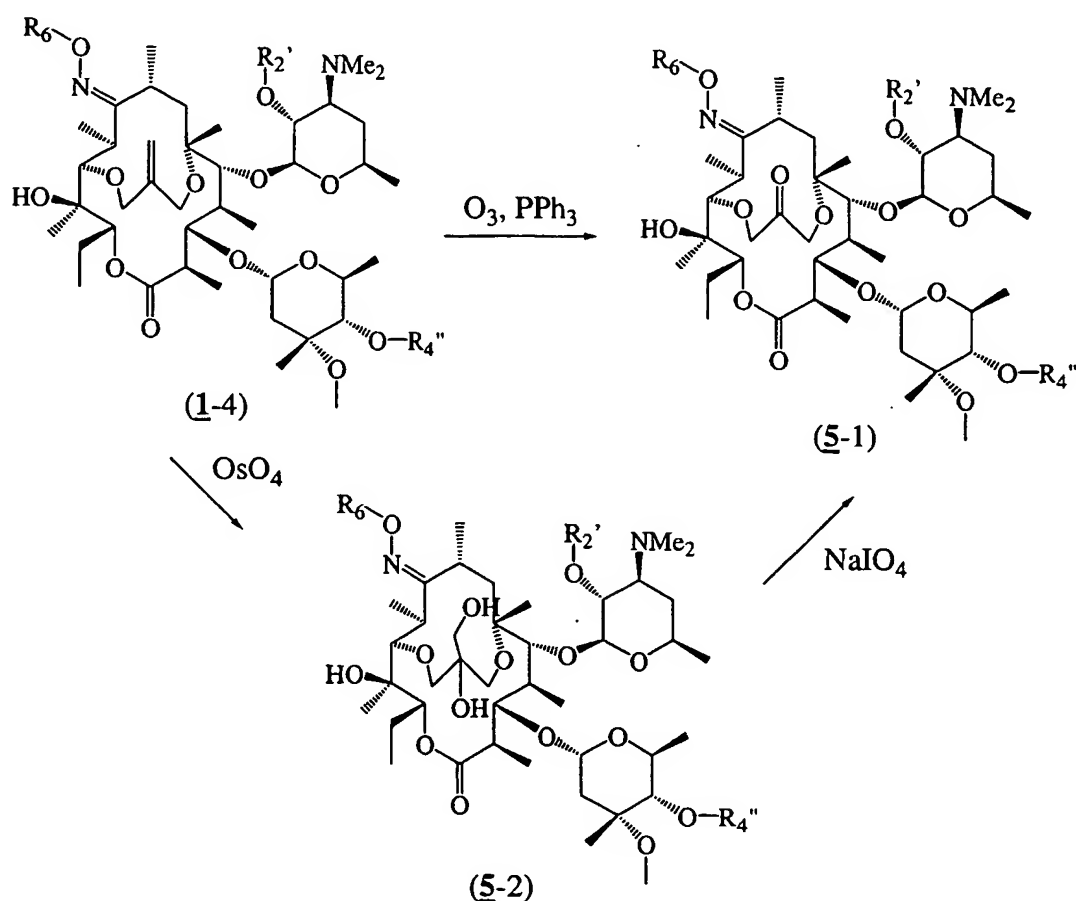
Typical bases include, but are not limited to, pyridine, triethylamine, diisopropyl ethylamine, N-methyl morpholine, N-methyl pyrrolidine, 2,6-lutidine, 1,8-diazabicyclo[5.4.0]undec-7-ene. For a more extensive discourse on acylating conditions see for example, T.W. Greene and P.G.M. Wuts in "Protective Groups in Organic Synthesis" 3rd ed., John Wiley & Son, Inc, 1999, referred to above herein.

Conversion of alkene (1-4) into ketone (5-1) can be accomplished by exposure of the alkene to ozone followed by decomposition of the ozonide with the appropriate reducing agent, as outlined in Scheme 5. The reaction is typically carried out in a solvent such as, but not limited to methanol, ethanol, ethyl acetate, glacial acetic acid, chloroform, methylene chloride or hexanes, preferably methanol, preferably at -20° to -78°C. Representative reducing agents are, for example, triphenylphosphine, trimethyl phosphite, thiourea, and

dimethyl sulfide, preferably triphenylphosphine. A more thorough discussion of ozonolysis and the conditions there for can be found in J. March "Advanced Organic Chemistry" 4th ed., Wiley & Son, Inc, 1992.

5

Scheme 5

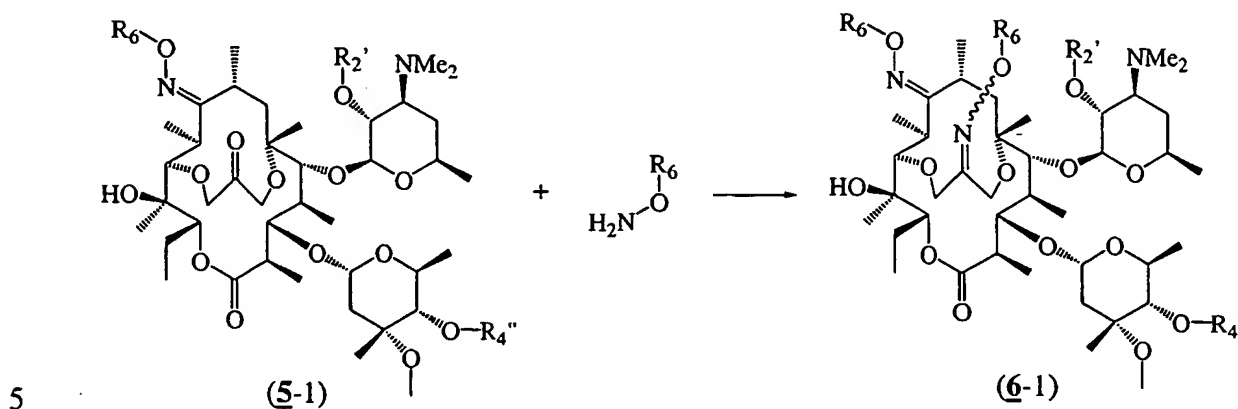


An alternative method for the preparation of ketone (5-1) involves dihydroxylation of the alkene followed by diol cleavage. The glycol (5-2) is first prepared by reacting the alkene (1-4) with osmium tetroxide. This reaction can be carried out either with stoichiometric amounts of osmium tetroxide, or with catalytic amounts of osmium tetroxide, if an oxidant such as hydrogen peroxide, tert-butyl hydroperoxide, or N-methylmorpholine-N-oxide is present. These reactions can be run in a variety of solvents including: 1,4-dioxane, tetrahydrofuran, tert-butanol and diethyl ether, preferably at 0° to 50 °C.

The glycol can be cleaved by a variety of reagents including, but not limited to, periodic acid, lead tetraacetate, manganese dioxide, potassium permanganate, sodium metaperiodate, and N-iodosuccinamide. Depending on the cleavage reagent, a variety of solvents can be used. Preferably the cleavage reagent is sodium metaperiodate, the solvent is

preferably a mixture of ethanol, methanol or 1,4-dioxane and water and the reaction temperature is 0°C to 25°C.

Scheme 6



Compounds of formula (5-1) represent useful intermediates which can be further functionalized in a variety of ways. Scheme 6 details a procedure for the conversion of the ketone (5-1) into an oxime of formula (6-1). Oxime formation can be accomplished under

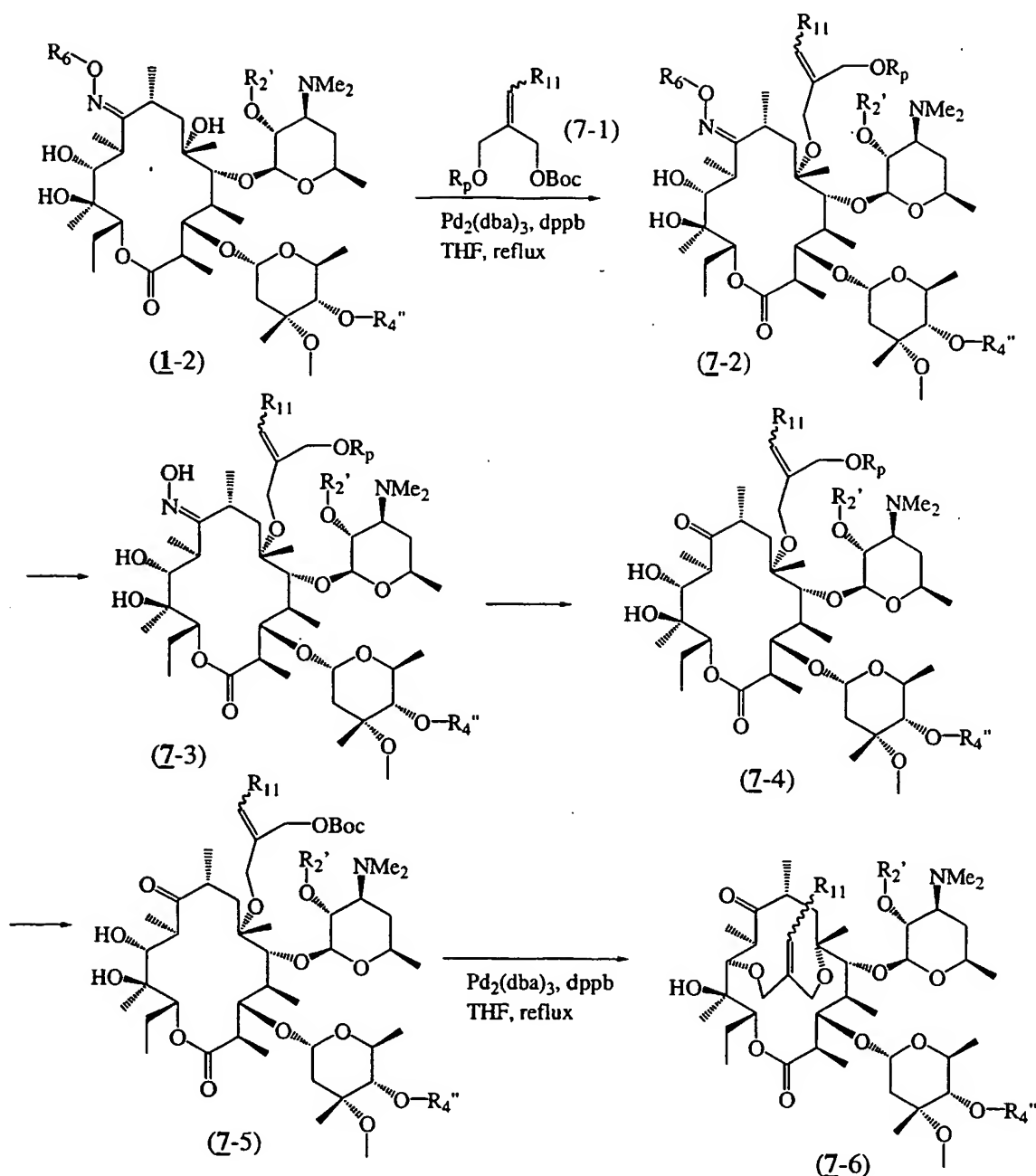
10 either acidic or basic conditions in a variety of solvents. Representative acids include, but are not limited to, hydrochloric, phosphoric, sulfuric, *para*-toluenesulfonic, and pyridinium *p*-toluene sulfonate. Likewise bases which are useful are, for example, triethylamine, pyridine, diisopropylethyl amine, 1,5-lutidine, imidazole, and the like. Appropriate solvents include, but are not limited to, methanol, ethanol, water, tetrahydrofuran, 1,2-dimethoxyethane, and

15 ethyl acetate. Preferably the reaction is run in ethanol using triethylamine as the base. The reaction temperature is generally 25°C to 50°C and reaction time is 1 to 12 hours.

20

25

Scheme 7



Scheme 7 details a procedure for the stepwise formation of the 6-11 bridged
 5 macrolide of formula (7-6). In a similar manner as before, the procedure involves reacting a
 compound of formula (1-2) with a suitable alkylating agent. As before, the erythromycin
 derivative of formula (1-2) is reacted with an alkylating agent of the formula:



where R_{12} is $\text{C}_1\text{-C}_{12}$ -alkyl and R_p and R_{11} are as previously defined.

10 Most palladium (0) catalysts are expected to work in this process. Some palladium (II)
 catalysts, such as palladium (II) acetate, which is converted into a palladium (0) species *in-*

situ by the actions of a phosphine, will work as well. See, for example, Beller et al. *Angew. Chem. Int. Ed. Engl.*, 1995, 34 (17), 1848. The palladium catalyst can be selected from, but not limited to, the group consisting of palladium (II) acetate, tetrakis(triphenylphosphine)palladium (0), tris(dibenzylideneacetone)dipalladium, 5 tetradibenzylideneacetone)dipalladium and the like. Palladium on carbon and palladium (II) halide catalysts are less preferred than other palladium catalysts for this process.

Suitable phosphines include, but are not limited to, triphenylphosphine, bis(diphenylphosphino)methane, 1,2-bis(diphenylphosphino)ethane, 1,3-bis(diphenylphosphino)propane, 1,4-bis(diphenylphosphino)butane, 1,5- 10 bis(diphenylphosphino)pentane, and tri(o-tolyl)phosphine, and the like.

The reaction is carried out in an aprotic solvent, preferably at elevated temperature, preferably at or above 50°C. The aprotic solvents include, but are not limited to, tetrahydrofuran, N,N-dimethylformamide, dimethyl sulfoxide, N-methyl-2-pyrrolidone, hexamethylphosphoric triamide, 1,2-dimethoxyethane, methyl-*tert*-butyl ether, heptane, 15 acetonitrile, isopropyl acetate and ethyl acetate. The most preferred solvents are tetrahydrofuran and toluene.

The alkylating agents useful in the process of the invention are the mixed silyl ether carbonates (7-1). Generally, the alkylating agents have the formula (7-1), previously described. The preferred alkylating agents are those wherein R₁₂ is *tert*-butyl, isopropyl or 20 isobutyl and R_p is *tert*-butyl dimethyl silyl, triisopropyl silyl, *tert*-butyl diphenyl silyl or the like.

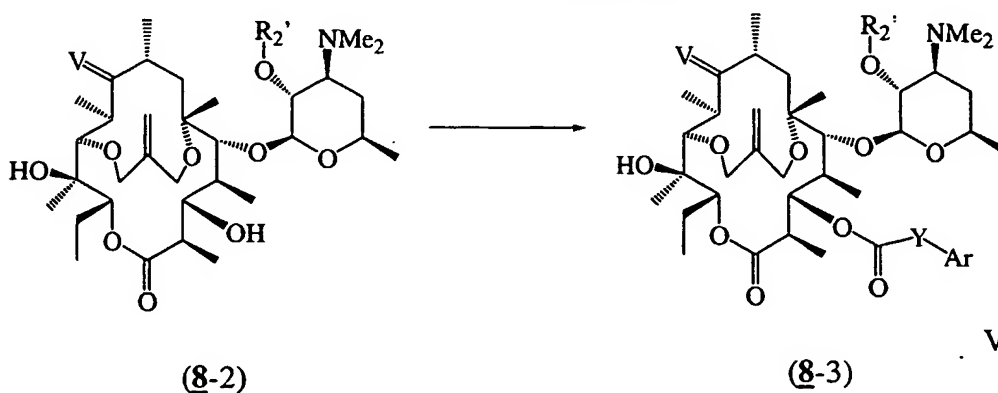
The alkylating reagents of formula (7-1) are prepared by reaction of a diol sequentially with a wide variety of compounds for incorporating the carbonate moiety, followed by a wide variety of compounds for incorporating the silyl moiety. Alkylating 25 reagents include, but are not limited to, *tert*-butyl chloroformate, di-*tert*-butyl dicarbonate, and 1-(*tert*-butoxycarbonyl)imidazole; whereas silylating reagents include, but are not limited to, *tert*-butyl dimethyl silyl chloride, *tert*-butyl dimethyl silyl triflate, *tert*-butyl dimethyl silyl cyanide, and *tert*-butyl dimethyl silyl imidazole. Both reactions are carried out in the presence of an organic or an inorganic base. The temperature of the reactions varies from 30 about -30°C to about 30°C. Preferably, the alkylating reagent is di-*tert*-butyl dicarbonate and the silylating reagent is *tert*-butyl dimethyl silyl chloride.

The free oxime (7-3) is prepared using essentially the same procedure as for the deprotection of oxime (1-4) where R₆ is Ac.

Compounds of formula (7-4) can be formed directly from compounds of formula (7-3) by the application of the previously described procedure for the reduction of oximes of formula (1-4), where R_6 is hydrogen, to the corresponding imine of formula (3-1) in Scheme 3.

The protecting group (Rp) is then removed from the hydroxyl of the compound of formula (7-4) using the appropriate conditions as outlined in T.W. Greene and P.G.M. Wuts in "Protective Groups in Organic Synthesis" 3rd ed., John Wiley & Son, Inc, 1999. For example, when the protecting group is TBS, tetra-*n*-butyl ammonium fluoride, hydrofluoric acid or trifluoroacetic acid may be used. Using standard conditions, the primary hydroxyl is converted to the *tert*-butyl carbonate, and subsequently the 11-hydroxyl group is alkylated by means of a palladium (0) catalyst as described previously. In this way compounds of formula (7-5) can be prepared readily.

Scheme 8



V: O or N-OR₆ or NC(O)
or NC(O)R₂

Y: O or (CH₂)_n or N, or S

n : 0-4

15

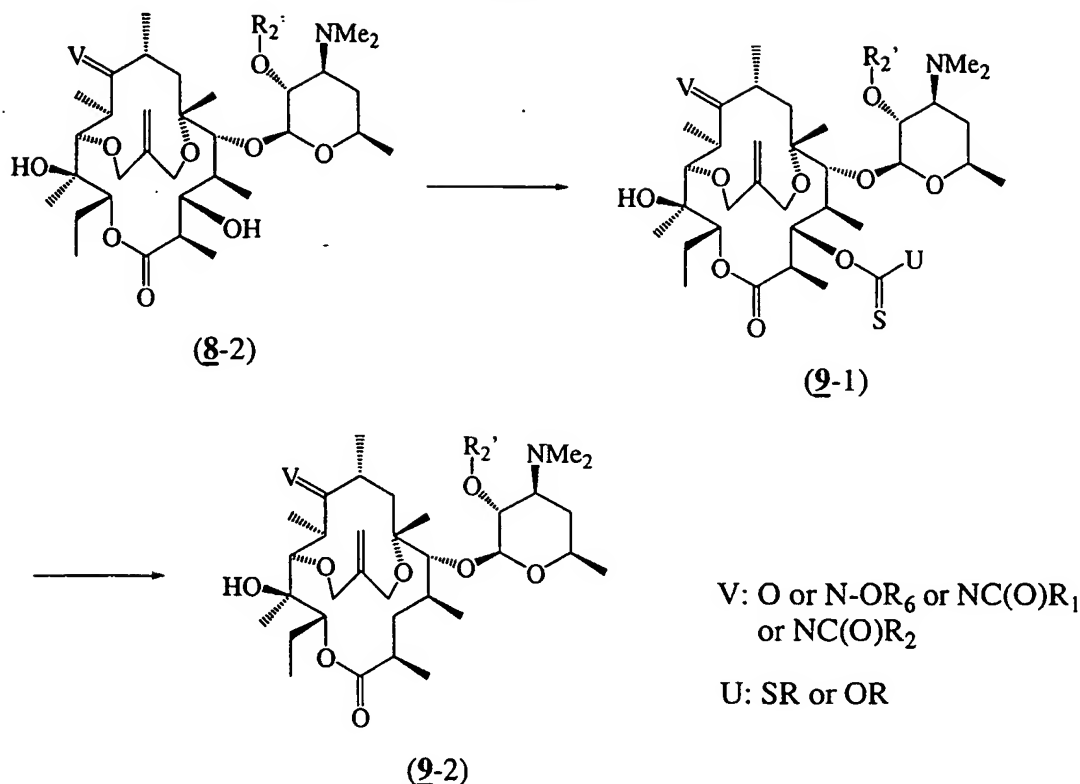
Scheme 8 illustrates a procedure for the acylation of the C-3 hydroxyl of compounds of formula (8-2). The hydroxyl group is acylated under basic conditions using a suitable acylating agent in an aprotic solvent. Typical acylating agents include, but are not limited to, acid chlorides, acid anhydrides, and chloroformates.

20

Typical bases include, but are not limited to, pyridine, triethylamine, diisopropyl ethylamine, N-methyl morpholine, N-methyl pyrrolidine, 2,6-lutidine, 1,8-diazabicyclo[5.4.0]undec-7-ene. For a more extensive discourse on acylating conditions see for example, T.W. Greene and P.G.M. Wuts in "Protective Groups in Organic Synthesis" 3rd ed., John Wiley & Son, Inc, 1999.

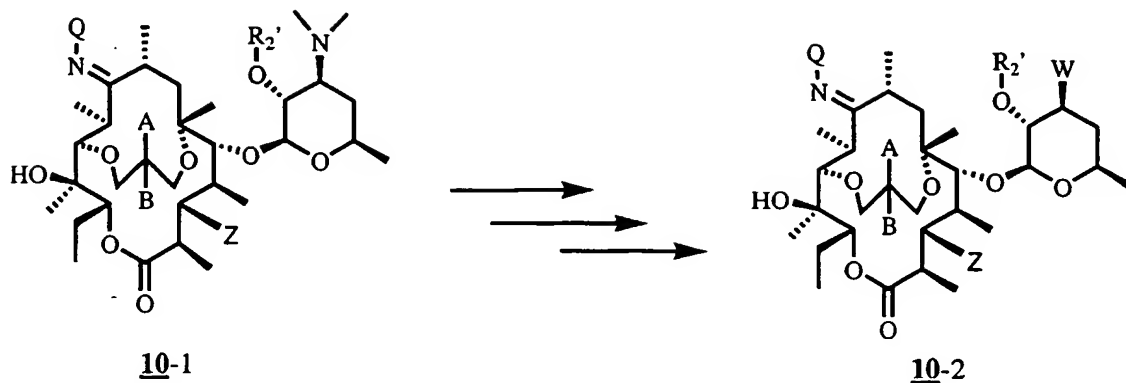
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Scheme 9



Another process of the invention, as illustrated in Scheme 9, involves the C-3
 5 deoxygenation of the macrolide (8-2) which can be accomplished via the two step procedure
 shown therein. In the first step the xanthate or thiocarbonate is formed by the reaction of
 alkoxide of alcohol (8-2) with the appropriate thiocarbonyl. For instance, formation of the
 xanthate can be accomplished by reaction of the alkoxide with either carbondisulfide
 followed by methyl iodide, or a dithiocarbonyl imidazole; whereas the thiocarbonate can be
 10 prepared by the reaction of the alkoxide with either thiocarbonyldimidazole followed by
 methanol, ethanol or the like, or a thiochloroformate. One skilled in the art will appreciate
 that other reagents and conditions exist to perform these transformations and that the
 examples above are for illustrative purposes only and do not limit the scope of this invention.
 These reactions are typically run in a polar aprotic solvent, preferably THF, acetonitrile, or
 15 DMF.

In the second step of Scheme 9, the thiocarbonate or xanthate is decomposed to give
 the alkane. Most typically this is done under radical conditions using, for example, a silyl
 hydride such as SiH(TMS)₃, SiH₂Ph₂ or the like, a tin hydride such as Bu₃SnH, Ph₃SnH or
 the like, and a radical initiator such as AIBN or *t*-butyl peroxide. The preferred solvent is
 20 toluene.

Scheme 10

It will be appreciated that compounds of the present invention include modification of the 3'-N of compounds of the formula (10-1). Compounds of formula (10-2) can be made via the methods delineated in U.S. Patents 6,034,069 and 6,387,885.

All references cited herein, whether in print, electronic, computer readable storage media or other form, are expressly incorporated by reference in their entirety, including but not limited to, abstracts, articles, journals, publications, texts, treatises, internet web sites, databases, patents, and patent publications.

Examples

The compounds and processes of the present invention will be better understood in connection with the following examples, which are intended as an illustration only and not limiting of the scope of the invention. Various changes and modifications to the disclosed embodiments will be apparent to those skilled in the art and such changes and modifications including, without limitation, those relating to the chemical structures, substituents, derivatives, formulations and/or methods of the invention may be made without departing from the spirit of the invention and the scope of the appended claims.

Example 1

Compound of formula IV: A and B taken together with the carbon atom to which they are attached = C=CH₂, Q = OH, R₂' is H, and R₄'' = Ac.

Step 1a: Compound of formula 1-2: R₆ = Ac, R₂' = Ac and R₄'' = Ac:

Acetic anhydride (35.9 ml, 0.38 mol), triethylamine (55.7 ml, 0.4 mol) and DMAP (3.7 g, 0.03 mol) were added to a solution of the compound of formula (1-2) where R₆ = R₂' = R₄'' = H (74.9 g, 0.1 mol) in 400 ml of THF at room temperature and the resulting mixture

was stirred at room temperature for about 16 hours. The reaction mixture was concentrated to about 200 ml under reduced pressure, diluted with 300 ml of ethyl acetate, washed with saturated NaHCO_3 (4X500 ml) and brine (500 ml). The organic phase was dried over sodium sulfate and the solvent was removed *in vacuo*. The solid residue was recrystallized from ethyl acetate to give the title compound (78g).

MS (ESI) m/z : 875.46 ($M+H$)⁺.

^{13}C -NMR(100 MHz, CDCl_3): δ 178.5, 175.4, 170.6, 170.2, 168.2, 100.2, 96.1, 83.3, 79.3, 78.7, 75.2, 74.5, 72.9, 70.0, 67.6, 63.4, 63.2, 60.6, 49.5, 44.7, 40.9, 35.4, 31.8, 28.5, 22.8, 21.7, 21.6, 21.5, 21.3, 21.2, 21.1, 19.9, 18.6, 18.4, 16.7, 14.9, 14.4, 14.3, 10.8, 9.2

10 Step 1b: Compound of formula 1-4: $R_6 = \text{Ac}$, $R_2' = \text{Ac}$ and $R_4'' = \text{Ac}$.

A mixture of the compound from step 1a (21.9 g, 25 mmol), 2-methylene-1,3-propane-[bis-(tert-butyl)carbonate] (18.02 g, 62.25 mmol) and 1,4-bis(diphenylphosphino)butane (640 mg, 1.5 mmol) was dissolved in freshly distilled THF (250 ml). To the solution was added $\text{Pd}_2(\text{dba})_3$ (687 mg, 0.75 mmol). The reaction mixture was heated to reflux slowly. After refluxing for 14 hours, the reaction was cooled to room temperature, diluted with 400 ml ethyl acetate, and washed with saturated NaHCO_3 (400 ml) and brine (400 ml). The organic phase was dried over Na_2SO_4 , the solvent was removed *in vacuo* and the solid residue was purified by silica gel chromatography (acetone : hexane/1:2) to give the title compound (22g). MS (ESI) m/z : 927.64 ($M+H$)⁺.

20 ^{13}C -NMR(100 MHz, CDCl_3): δ 176.5, 175.9, 170.7, 170.1, 169.9, 141.6, 124.7, 100.4, 96.0, 79.1, 78.7, 78.2, 78.0, 77.4, 76.5, 73.5, 73.0, 72.4, 72.1, 67.8, 66.1, 63.4, 63.3, 49.6, 44.1, 41.2, 40.9, 37.3, 35.4, 35.1, 31.3, 29.5, 28.5, 27.1, 23.4, 21.7, 21.3, 21.1, 20.9, 20.3, 18.8, 18.3, 17.4, 15.7, 13.4, 12.7, 8.6.

25 Step 1c: Compound of formula IV: A and B taken together with the carbon atom to which they are attached = $\text{C}=\text{CH}_2$, $\text{O} = \text{OH}$, $R_2' = \text{H}$, and $R_4'' = \text{Ac}$.

A solution of the compound from step 1b (22g) in 400 ml methanol was refluxed for 48 hours. The solvent was removed *in vacuo* and the compound was purified by column chromatography (CH_2Cl_2 : 2M ammonia in $\text{MeOH}/95:5$) to give the title compound (18.5 g). MS (ESI) m/z : 843.67 ($M+H$)⁺.

30 ^{13}C -NMR(100 MHz, CDCl_3): δ 176.2, 170.8, 168.8, 142.0, 124.2, 102.5, 95.9, 79.4, 78.7, 78.1, 78.0, 76.6, 73.0, 71.8, 71.1, 68.2, 65.6, 63.2, 49.7, 44.2, 41.7, 40.5, 37.7, 35.0, 34.4, 29.3, 25.8, 23.5, 21.9, 21.3, 21.1, 19.0, 18.1, 17.5, 15.3, 13.2, 12.7, 8.7.

Example 2

Compound of formula IV: A and B taken together with the carbon atom to which are attached = C=CH₂, Q = H, R₂' = H, and R₄'' = Ac.

Formic acid (2.33 ml, 61.7 mmol), water (115 ml) and sodium thiosulfate (9.7g, 55.5 mol) were added sequentially into a solution of the title compound of example 1 (15.6 g, 18.5 mmol) in isopropanol (10 ml) at room temperature. The reaction mixture was refluxed for 1.5 hour, cooled to room temperature, diluted with ethyl acetate (300 ml), and washed with saturated sodium bicarbonate (2x200 ml) and brine (200 ml). The organic phase was dried over sodium sulfate and the solvent was removed *in vacuo*. The residue was purified by silica gel chromatography to give the title compound (8.0g).

MS (ESI) m/z: 827.59 (M+H)⁺.

¹³C-NMR(100 MHz, CDCl₃): δ 190.8, 176.6, 170.7, 142.5, 122.2, 102.4, 96.0, 95.9, 79.9, 78.9, 78.7, 77.9, 76.3, 72.9, 71.1, 68.2, 65.5, 63.2, 50.3, 49.7, 44.5, 41.5, 40.5, 37.5, 35.4, 35.0, 29.1, 23.2, 21.9, 21.4, 21.3, 21.1, 19.8, 18.1, 17.2, 14.6, 13.7, 12.4, 8.8.

Example 3

Compound of formula V: A and B taken together with the carbon atom to which they are attached = C=CH₂, Q = H, and R₂' = H.

Method 1

Hydrochloric acid (0.5N, 60 ml) was added to a solution of the compound from Example 2 (5.8 g, 7 mmol) in ethanol (30 ml) at room temperature. The mixture was heated to 65°C for 2 hours, cooled to room temperature and the pH was adjusted to pH=10 by slow addition of 3N aqueous sodium hydroxide. The aqueous solution was extracted with ethyl acetate (200ml) and the organic phase was washed once with saturated sodium bicarbonate (200 ml), dried over sodium sulfate and solvent was removed *in vacuo*. The residue was purified by silica gel chromatography (CH₂Cl₂: 2M ammonia in methanol/95:5) to give the title compound (2.8 g).

MS (ESI) m/z: 627.56(M+H)⁺.

¹³C-NMR(100 MHz, CDCl₃): δ 188.5, 176.0, 143.9, 118.9, 106.9, 90.8, 79.8, 79.6, 79.2, 77.4, 75.9, 75.3, 70.8, 70.4, 65.8, 65.3, 44.6, 42.1, 40.4, 38.6, 36.4, 35.3, 28.2, 22.9, 21.5, 20.0, 19.7, 16.8, 15.1, 14.9, 11.5, 8.3.

Method 2

Titanium trichloride (40 ml, 20% in 3% hydrochloric acid) was added dropwise during 10 minutes into a stirred solution of the compound from step 1c (9.5 g, 11.3 mmol) and ammonia acetate (17.4 g, 226 mmol) in 120 ml of methanol at 0°C. The reaction mixture was allowed to warm up to room temperature and stirred overnight. The pH of the reaction mixture was adjusted to pH=10 by slow addition of 3N aqueous sodium hydroxide. The aqueous solution was extracted with ethyl acetate (200 ml) and the organic phase was washed once with saturated sodium bicarbonate (200ml), dried over sodium sulfate and solvent was removed *in vacuo*. The residue was purified by silica gel chromatography (CH₂Cl₂: 2M ammonia in methanol/95:5) to give the title compound (3.0 g).

MS (ESI) m/z: 627.56 (M+H)⁺.

Example 4

Compound of formula V: A and B taken together with the carbon atom to which they are attached = C=CH₂, Q = Ac, and R₂' = H.

Step 4a: Compound of formula V: A and B taken together with the carbon atom to which they are attached = C=CH₂, Q = Ac, and R₂' = Ac.

Acetic anhydride (1.36 ml, 14.4 mmol) was added to a solution of the title compound of Example 3 (3 g, 4.8 mmol) and triethylamine (2.8 ml, 20 mmol) in dichloromethane (40 ml). The reaction mixture was stirred at room temperature for 4 hours, diluted with 100 ml of dichloromethane and washed with saturated sodium bicarbonate (3x100 ml) and brine (100 ml). The organic phase was dried over sodium sulfate and the solvent was removed *in vacuo*. The residue was purified by silica gel chromatography (hexanes:acetone/1:1) to give title compound (2.9 g).

MS (ESI) m/z: 711.50 (M+H)⁺.

¹³C-NMR(100 MHz, CDCl₃): δ 184.7, 176.9, 174.9, 170.1, 141.9, 122.2, 99.4, 81.2, 79.0, 77.8, 77.7, 76.1, 73.5, 71.7, 68.8, 65.7, 63.2, 43.7, 40.8, 39.9, 38.2, 36.2, 35.6, 31.0, 25.5, 23.2, 21.6, 21.2, 19.9, 19.5, 17.1, 15.8, 14.7, 11.8, 7.9.

Step 4b: Step 4a: Compound of formula V: A and B taken together with the carbon atom to which they are attached = C=CH₂, Q = Ac, and R₂' = H.

The title compound is prepared by refluxing the compound from step 4a in methanol according to the procedure described in Example 1 (Step 1c).

Example 5

Compound of formula IV: A and B taken together with the carbon atom to which they are attached = C=CH₂, Q = O-CH₂OCH₃, R₂' = H, and R₄'' = Ac.

5 Step 5a: Compound of formula IV: A and B taken together with the carbon atom to which they are attached = C=CH₂, Q = OH, R₂' = Ac, and R₄'' = Ac.

1M LiOH (10 ml) was added to a solution of the compound from step 1b (1.85g, 2 mmol) in 10 ml THF and 10 ml isopropanol at room temperature. After stirring at room temperature for 30 minutes, the reaction mixture was diluted with saturated sodium bicarbonate (40 ml) and extracted with ethyl acetate (2x40 ml). The organic phase was
10 washed with brine (2x 40 ml), dried over sodium sulfate and the solvent was removed *in vacuo*. The residue was purified by silica gel chromatography (hexanes:acetone, 1:1) to give the title compound (1.65g).

MS (ESI) m/z: 885.45 (M+H)⁺.

¹³C-NMR(100 MHz, CDCl₃): δ 175.9, 170.7, 170.1, 168.7, 142.0, 142.2, 100.5, 95.9, 79.4,
15 78.6, 78.1, 77.9, 76.6, 73.0, 72.8, 72.0, 71.7, 67.7, 65.5, 63.5, 63.2, 49.6, 44.1, 41.4, 40.9, 37.4, 35.0, 34.4, 31.7, 31.3, 25.7, 23.5, 21.7, 21.3, 19.0, 18.1, 17.5, 15.3, 13.2, 12.7, 8.6

Step 5b: Compound of formula IV: A and B taken together with the carbon atom to which they are attached = C=CH₂, Q = O-CH₂OCH₃, R₂' = Ac, and R₄'' = Ac.

Sodium hydride (33 mg, 1.3 mmol) was added into a solution of the title compound of
20 example 5a (885 mg, 1 mmol) in 10 ml DMF at 0°C. MOM-Cl (90 µl, 1.2 mmol) was added and stirred at 0°C overnight. The reaction mixture was diluted with ethyl acetate (20 ml) and quenched with saturated NaHCO₃, washed with brine (20 ml) and dried over anhydrous sodium sulfate. The residue was purified by silica gel chromatography to give the title compound (0.4 g).

25 MS (ESI) m/z: 929.49 (M+H)⁺.

¹³C-NMR(100 MHz, CDCl₃): δ 175.9, 170.7, 170.1, 169.5, 142.1, 124.5, 100.5, 98.4, 96.0, 79.3, 78.7, 78.2, 78.1, 77.2, 76.5, 72.9, 72.0, 71.8, 67.7, 65.9, 63.4, 63.2, 56.6, 49.6, 44.1, 41.4, 40.9, 37.2, 35.0, 34.8, 34.6, 31.3, 28.0, 27.0, 25.4, 23.4, 21.7, 21.3, 21.1, 20.8, 19.0, 18.2, 17.4, 15.5, 13.3, 12.7, 8.6.

30 Step 5c: Compound of formula IV: A and B taken together with the carbon atom to which they are attached = C=CH₂, Q = O-CH₂OCH₃, R₂' = H, and R₄'' = Ac.

The title compound was prepared by refluxing the compound from Step 5b in methanol according to the procedure described in Example 1 (Step 1c).

MS (ESI) m/z : 887 (M+H)⁺.

Example 6

Compound of formula V: A and B taken together with the carbon atom to which they are
5 attached = C=CH₂, Q = O-CH₂OCH₃, and R₂' = H.

Step 6a: Compound of formula v: A and B taken together with the carbon atom to
which they are attached = C=CH₂, Q = OH, and R₂' = Ac.

To a solution of the title compound of example 1 (4.2 g, 4.5 mmol) in 50 ml methanol
was added 2M HCl (10 ml). The reaction mixture was refluxed for 1.5 hours and then
10 condensed to 30 ml. Saturated sodium bicarbonate (30 ml) was added and the mixture was
extracted with ethyl acetate (50 ml). The organic phase was dried over sodium sulfate and
solvent was removed *in vacuo*. The residue was purified by silica gel chromatography
(hexane:acetone/1:1) to give the title compound (2.5g).

MS (ESI) m/z : 685.45 (M+H)⁺.

15 ¹³C-NMR(100 MHz, CDCl₃): δ 175.2, 170.2, 166.3, 143.6, 119.3, 99.6, 82.2, 79.5, 78.1,
77.5, 76.0, 73.7, 71.7, 68.9, 65.5, 63.3, 43.8, 40.8, 37.4, 35.9, 34.3, 31.1, 25.6, 23.3, 21.7,
21.3, 19.9, 19.6, 17.1, 15.7, 14.7, 11.9, 7.9

Step 6b: Compound of formula I: A and B taken together with the carbon atom to
which they are attached = C=CH₂, Q = O-CH₂CH₃, and R₂' = Ac.

20 To a solution of the compound from step 6a (6.85g, 10 mmol) in 40 ml DMF was
added NaH (303 mg, 1.3 mmol) at 0°C portion wise. After 10 minutes, MOM-Cl (900 µl,
1.15 mmol) was added at 0°C during 15 minutes. The reaction mixture was stirred at 0°C for
16 hours, diluted with ethyl acetate (100 ml) and quenched with saturated sodium bicarbonate
(60 ml). The organic layer was separated, washed with brine (60 ml) and dried over sodium
25 sulfate. The solvent was removed on *vacuo* and the residue was purified by silica gel
chromatography (hexane:acetone/1:1) to give the title compound (4.5 g).

MS (ESI) m/z : 729 (M+H)⁺.

Step 6c. Compound of formula I: A and B taken together with the carbon atom to
which they are attached = C=CH₂, Q = O-CH₂OCH₃, and R₂' = H.

30 The title compound of Example 6 was prepared by refluxing the compound from Step
6b in methanol according to the procedure described in Example 1 (Step 1c).

MS (ESI) m/z : 687 (M+H)⁺.

Example 7

Compound of formula I: A and B taken together with the carbon atom to which they are attached = C=CH₂, X and Y taken together with the carbon atom to which they are attached = C=NAc, L = CH₂CH₃, W is N(CH₃)₂, Z = H and R₂' = H

- 5 Step 7a: Compound of formula I: A and B taken together with the carbon atom to which they are attached = C=CH₂, X and Y taken together with the carbon atom to which they are attached = C=NAc, L = CH₂CH₃, W is N(CH₃)₂, Z = H and R₂' = Ac.

The title compound is prepared from the compound of Step 4a, sodium hydride, carbon disulfide and tri-n-butyl tin hydride according to the procedures described in the literature. For further details, see Elliott, Richard L.; Pireh, Daisy; Griesgraber, George; Nilius, Angela M.; Ewing, Patty J.; Bui, Mai Ha; Raney, Patti M.; Flamm, Robert K.; Kim, Ki; Henry, Rodger F.; Chu, Daniel T. W.; Plattner, Jacob J.; Or, Yat Sun. J. Med. Chem. (1998), 41(10), 1651-1659.

- 15 Step 7b: Compound of formula I: A and B taken together with the carbon atom to which they are attached = C=CH₂, X and Y taken together with the carbon atom to which they are attached = C=NAc, L = CH₂CH₃, W is N(CH₃)₂, Z = H and R₂' = H.

The title compound is prepared by refluxing the compound from step 7a in methanol according to the procedure described in Example 1 (Step 1c).

20 **Example 8**

Compound of formula I: A and B taken together with the carbon atom to which they are attached = C=CH₂, X and Y taken together with the carbon atom to which they are attached = C=NAc, L = CH₂CH₃, Z = OC(O)(p-nitrophenyl) and R₂' = H.

- 25 Step 8a: Compound of formula I: A and B taken together with the carbon atom to which they are attached = C=CH₂, X and Y taken together with the carbon atom to which they are attached = C=NAc, L = CH₂CH₃, W is N(CH₃)₂, Z = OC(O)(p-nitrophenyl) and R₂' = Ac.

The title compound is prepared from the compound of Step 4a of Example 4, sodium hydride, and para-nitrobenzoyl fluoride according to the procedures described in the literature. For further details, see Misawa et al, 6-O-Desosaminylerthronolide derivatives, U.S. Patent No. 5,602,239.

Step 8b. Compound of formula I: A and B taken together with the carbon atom to which they are attached = C=CH₂, X and Y taken together with the carbon atom to

which they are attached = C=NAc, L = CH₂CH₃, W is N(CH₃)₂, Z = OC(O)(p-nitrophenyl) and R₂' = H.

The title compound is prepared by refluxing the compound from step 8a in methanol according to the procedure described in Example 1 (Step 1c).

5

Example 9

Compound of formula I: A and B taken together with the carbon atom to which they are attached = C=CH₂, X and Y taken together with the carbon atom to which they are attached = C=NAc, L = CH₂CH₃, W is N(CH₃)₂, Z = OC(O)[2-(NO₂), 4-(CF₃)Phenyl] and R₂' = H.

10

The title compound is prepared from the compound of Step 4a of Example 4, 2-nitro-4-trifluoromethylbenzoyl fluoride and sodium hydride followed by reaction in methanol according to the procedures described in Example 8.

Example 10

15

Compound of formula I: A and B taken together with the carbon atom to which they are attached = C=CH₂, X and Y taken together with the carbon atom to which they are attached = C=NAc, L = CH₂CH₃, W is N(CH₃)₂, Z = OC(O)CH₂(p-methoxyphenyl) and R₂' = H.

20

Step 10a: Compound of formula I: A and B taken together with the carbon atom to which they are attached = C=CH₂, X and Y taken together with the carbon atom to which they are attached = C=NAc, L = CH₂CH₃, W is N(CH₃)₂, Z = OC(O)CH₂(p-methoxyphenyl) and R₂' = Ac.

The title compound is prepared from the compound of Step 4a of Example 4, p-methoxyphenyl acetic acid, pivaloyl chloride, and triethylamine in a solution of pyridine and dichloromethane according to the procedure described in the literature. For further details, see

25

Morimoto et al, 5-O-Desosaminylerythronolide derivatives, EP 0619320, and WO 99/21868.

Step 10b: Compound of formula I: A and B taken together with the carbon atom to which they attached = C=CH₂, X and Y taken together together with the carbon atom to which they are attached = C=NAc, L = CH₂CH₃, W is N(CH₃)₂, Z = OC(O)CH₂(p-methoxyphenyl) and R₂' = H.

30

The title compound is prepared by refluxing the compound from Step 10a in methanol according to the procedure described in Example 1 (Step 1c).

Example 11

Compound of formula IV: A and B taken together with the carbon atom to which they are attached = C=CH₂, Q = Ac, R₂' = H, and R₄'' = Ac.

5 Step 11a. Compound of formula IV: A and B taken together with the carbon atom to which they are attached = C=CH₂, Q = Ac, R₂' = Ac, and R₄'' = Ac.

The title compound was prepared from the title compound of Example 6, acetic anhydride, triethylamine and dimethylaminopyridine according to the procedures described in Example 4 (Step 4a).

MS (ESI) m/z: 911 (M+H)⁺.

10 Step 11b. Compound of formula IV: A and B taken together with the carbon atom to which they are attached = C=CH₂, Q = Ac, R₂' = H, and R₄'' = Ac.

The title compound of Example 11 is prepared by refluxing the compound from Step 11a in methanol according to the procedure described in Example 1 (Step 1c).

15 Example 12

Compound of formula I: Compound of formula IV: A and B taken together with the carbon atom to which they are attached = C=O, Q = Ac, R₂' = H, and R₄'' = Ac.

Ozone is bubbled into a solution of the title compound of Example 11 in methanol and dichloromethane at -78 °C until the solution turns light blue. Excess ozone is removed by
20 bubbling with nitrogen. Triphenylphosphine is added and the solution is allowed to warm up to room temperature. The solvent is removed *in vacuo* and the solid residue is re-dissolved in tetrahydrofuran. The resulting solution is refluxed overnight. The title compound of Example 12 is purified by silica gel chromatography.

25 Example 13

Compound of formula IV: A and B taken together with the carbon atom to which they are attached = C=OBz, Q = Ac, R₂' = H, and R₄'' = Ac.

O-benzyl hydroxylamine and the title compound of Example 12 are dissolved in ethanol. The reaction mixture is stirred at room temperature for 1 hour. The solvent is
30 removed and the title compound is purified by silica gel chromatography.

Example 14

Compound of formula IV: A and B taken together with the carbon atom to which they are attached = C=(3-quinolyl), Q = Ac, R₂' = H, and R₄'' = Ac.

The title compound is prepared from the title compound of Example 13, 18, 3-bromoquinoline, and palladium (II) catalyst according to the procedures described in the literature. For further details, see Or, Yat Sun; Clark, Richard F.; Wang, Sanyi; Chu, Daniel T. W.; Nilius, Angela M.; Flamm, Robert K.; Mitten, Michael; Ewing, Patty; Alder, Jeff; Ma, Zhenkun. *J. Med. Chem.* (2000), 43(6), 1045-1049.

Example 15

Compound of formula I: A and B taken together with the carbon atom to which they are attached = C=CH₂, X and Y taken together with the carbon atom to which they are attached = C=O, L = CH₂CH₃, W is N(CH₃)₂, Z = 4-acetoxycladinoside and R₂' = H

Step 15a: Compound of formula 7-2: R₆ = Ac, R₁₁ = H, R_p = *tert*-butyldimethylsilyl, R₂' = Ac, and R₄'' = Ac.

tert-Butyl-OC(O)-OCH₂(C=CH₂)CH₂-O-*tert*-butyldimethylsilyl (0.9 g, 3 mmol) and 1,4-bis(diphenylphosphino)butane (170 mg, 0.4 mmol) and Pd₂(dba)₃ (183 mg, 0.2 mmol) were added into a solution of the compound of formula (1-2), R₆ = R₂' = R₄'' = Ac (1.75 g, 2 mmol) in tetrahydrofuran (10 ml) at room temperature. The reaction mixture was refluxed under nitrogen overnight, cooled to room temperature and the solvent was removed *in vacuo*. The residue was purified by silica gel chromatography (acetone:hexane/1:3) to give the title compound (1.5 g).

MS (ESI) m/z: 1059.65 (M+H)⁺.

¹³C-NMR(100 MHz, CDCl₃): δ 181.2, 179.3, 175.9, 175.5, 173.5, 148.5, 116.5, 104.8, 102.0, 85.2, 84.3, 83.9, 83.6, 82.8, 82.2, 79.7, 78.1, 77.6, 75.6, 72.4, 70.4, 69.0, 68.6, 54.6, 49.9, 46.2, 43.2, 40.8, 36.5, 33.6, 31.4, 27.1, 27.0, 26.6, 26.3, 25.2, 25.1, 24.0, 23.7, 22.0, 20.4, 16.0, 15.2, 0.5, 0.0

Step 15b: Compound of formula 7-2: R₆ = H, R₁₁ = H, R_p = *tert*-butyldimethylsilyl, R₂' = H, and R₄'' = Ac.

A solution of the compound from Step 15a (3.18 g, 3 mmol) in methanol (80 ml) was refluxed for 8 hours. The reaction was cooled to room temperature, the solvent was removed *in vacuo* and the residue was purified by silica gel chromatography (2M ammonia in methanol: dichloromethane/3:97) to give the title compound (2.6 g).

MS (ESI) m/z : 975.47 (M+H)⁺.

¹³C-NMR(100 MHz, CDCl₃): δ 179.5, 178.9, 175.7, 150.6, 121.5, 106.8, 101.4, 85.3, 83.9, 83.7, 82.4, 82.0, 79.3, 77.8, 76.7, 76.5, 72.7, 70.4, 70.1, 69.3, 68.3, 54.6, 49.8, 45.5, 43.0, 42.9, 40.6, 38.1, 34.0, 31.1, 30.5, 27.1, 26.3, 26.1, 26.0, 24.3, 23.7, 23.5, 21.5, 19.9, 15.7, 14.8, 0.5, 0.0.

Step 15c: Compound of formula 7-4: R₁₁ = H, R_p = H, R₂' = H, and R₄'' = Ac.

Formic acid (0.38 ml, 10 mmol) and Na₂S₂O₄ (1.39, 8 mmol) was added into an emulsion of the compound from Step 15 b (2.44g, 2.5 mmol) in isopropanol (25 ml) and water (30 ml). The mixture was heated to 90 °C and stirred at that temperature for 8 hours. The reaction mixture was cooled to room temperature, diluted with ethyl acetate (60 ml), washed with saturated sodium bicarbonate (3x60 ml), and dried over sodium sulfate. The solvent was removed *in vacuo* and the residue was purified by silica gel chromatography (2M ammonia in methanol:dichloromethane/3: 97) to give the title compound (1.7 g).

MS (ESI) m/z : 846.54 (M+H)⁺.

¹³C-NMR(100 MHz, CDCl₃): δ 221.3, 175.3, 170.6, 147.0, 114.1, 101.8, 96.6, 79.9, 79.2, 78.8, 78.7, 77.4, 75.0, 72.8, 71.4, 68.8, 67.8, 65.4, 65.3, 63.7, 63.4, 60.6, 49.6, 45.5, 44.8, 40.4, 38.2, 38.0, 35.6, 22.0, 21.2, 21.1, 19.6, 18.6, 16.5, 14.4, 12.2, 10.6, 9.8.

Step 15d: Compound of formula 7-4: R₁₁ = H, R_p = H, R₂' = Ac, and R₄'' = Ac.

Acetic anhydride (94 μ l, 1 mmol) was added to a solution of the compound from Step 15c (338.4mg, 0.4 mmol) in dichloromethane (5 ml). The mixture was stirred at room temperature for 16 hours. The solvent was removed *in vacuo* and the residue was purified by silica gel chromatography (acetone:hexane/4 : 6) to give the title compound (330 mg).

MS (ESI) m/z : 888.58 (M+H)⁺.

¹³C-NMR(100 MHz, CDCl₃): δ 221.3, 175.1, 170.6, 170.3, 146.8, 114.2, 99.6, 96.5, 79.9, 79.1, 78.5, 78.4, 77.1, 74.9, 72.8, 72.1, 68.9, 67.1, 65.1, 63.7, 63.5, 63.1, 49.3, 45.5, 44.8, 40.6, 38.0, 37.7, 37.6, 35.5, 29.4, 21.8, 21.3, 21.1, 21.0, 19.4, 18.6, 16.6, 12.2, 10.6, 9.6.

Step 15e: Compound of formula 7-4: R₁₁ = H, R_p = *tert*-butoxycarbonyl, R₂' = Ac, and R₄'' = Ac.

Di-*tert*-butyl-dicarbonate (69 μ l, 0.3 mmol) was added to a solution of the compound of Step 15d (178 mg, 0.2 mmol) and triethylamine (56 μ l, 0.4 mmol) in dichloromethane (8 ml) at room temperature. After 10 minutes, N,N-dimethylamino pyridine (12.2 mg, 0.1 mmol) was added. The resulting solution was stirred at room temperature for 2 hours. The

solvent was removed *in vacuo* and the residue was purified by silica gel chromatography (acetone:hexane/1:3) to give the title compound (180 mg).

MS (ESI) m/z : 988.41 (M+H)⁺.

¹³C-NMR(100 MHz, CDCl₃): δ 219.6, 174.6, 170.6, 170.3, 153.8, 141.3, 116.8, 99.6, 96.5, 82.0, 80.2, 79.4, 78.7, 78.6, 76.8, 74.9, 72.9, 72.4, 69.1, 67.9, 67.2, 64.8, 63.6, 63.4, 49.4, 45.2, 44.8, 41.0, 37.9, 37.7, 37.6, 35.6, 31.8, 31.3, 31.2, 28.2, 28.1, 22.9, 21.8, 21.5, 21.4, 21.1, 19.4, 18.7, 16.7, 16.6, 14.4, 12.5, 10.7, 9.7.

Step 15f: Compound of formula I: A and B taken together with the carbon atom to which they are attached = C=CH₂, X and Y taken together with the carbon atom to which they are attached = C=O, L = CH₂CH₃, W is N(CH₃)₂, Z = 4-acetoxycladinose and R₂' = Ac.

1,4-bis(diphenylphosphino)butane (8.5 mg, 0.02 mmol) and Pd₂(dba)₃ (9.2 mg, 0.01 mmol) were added to a solution of the compound of Step 15e (98.8 mg, 0.1 mmol) in 2 ml anhydrous THF at room temperature. The resulting mixture was refluxed for 30 minutes. The solvent was removed *in vacuo* and the residue was used for next step reaction without purification.

MS (ESI) m/z : 870.49 (M+H)⁺.

Step 15g. Compound of formula I: A and B taken together with the carbon atom to which they are attached = C=CH₂, X and Y taken together with the carbon atom to which they are attached = C=O, L = CH₂CH₃, W is N(CH₃)₂, Z = 4-acetoxycladinose and R₂' = H.

A solution of the compound of Step 15f (87 mg, 0.01 mmol) in 5 ml methanol was refluxed for 8 hours. The solvent was removed *in vacuo* and the residue was purified by silica gel chromatography (CH₂Cl₂ : 2M ammonia in CH₃OH/97:3) to give the title compound (70 mg).

MS (ESI) m/z : 828.50 (M+H)⁺.

¹³C-NMR(100 MHz, CDCl₃): δ 219.1, 176.01, 170.8, 141.03, 125.7, 102.7, 96.0, 79.2, 78.8, 77.9, 77.2, 76.9, 73.0, 72.3, 71.1, 70.2, 68.4, 65.8, 65.6, 63.3, 49.9, 46.6, 44.5, 41.9, 40.6, 39.4, 38.9, 35.2, 29.1, 23.3, 21.9, 21.4, 21.2, 20.7, 18.3, 17.9, 13.5, 12.6, 8.7.

Example 16

Compound of formula I: A and B taken together with the carbon atom to which they are attached = C=CH-quinolin-3-yl, X and Y taken together with the carbon atom to which they are attached = C=O, L = CH₂CH₃, W is N(CH₃)₂, Z = 4-acetoxycladinoses and R₂' = H.

- 5 To a solution of the title compound from Example 15 (992 mg, 1.2 mmol), 3-bromoquinoline (340 μ l, 2.5 mmol) and triethyl amine (836 μ l, 6 mmol) in acetonitrile (12 ml) was added P(o-Tol)₃ (146 mg, 0.48 mmol) and palladium acetate (54 mg, 0.24 mmol) at room temperature. The mixture was degassed and heated to 80°C and stirred for 16 hours. The mixture was diluted with ethyl acetate (50 ml) and washed with NaHCO₃ (60 ml x 2) and
- 10 brine (60 ml). The solvent was removed *in vacuo* and the residue was purified by silica gel chromatography (CH₂Cl₂ : 2M ammonia in CH₃OH/97:3) to give the title compound. MS (ESI) m/z: 955 (M+H)⁺.

Example 17

- 15 Compound of formula I: A and B taken together with the carbon atom to which they are attached = C=CH-quinolin-3-yl, X and Y taken together with the carbon atom to which they are attached = C=O, L = CH₂CH₃, W is N(CH₃)₂, Z = OH, and R₂' = H.

- To a solution of the title compound from Example 16 (150 mg, 0.16 mmol) in ethanol (3 ml) was added 5 ml of 5N HCl. The mixture was heated to 65°C and stirred for 2
- 20 hours. The reaction was quenched with saturated NaHCO₃ (25 ml) and extracted with ethyl acetate (25 ml). The extract was washed with brine and dried over anhydrous Na₂SO₄. The solvent was removed *in vacuo* and the residue was purified by silica gel chromatography (CH₂Cl₂ : 2M ammonia in CH₃OH/97:3) to give the title compound. MS (ESI) m/z: 755 (M+H)⁺.

25

Example 18

Compound of formula I: A and B taken together with the carbon atom to which they are attached = C=CH₂, X and Y taken together with the carbon atom to which they are attached = C=O, L = CH₂CH₃, W is N(CH₃)₂, Z = OH and R₂' = H.

- 30 Step 18a: Compound of formula I: A and B taken together with the carbon atom to which they are attached = C=CH₂, X and Y taken together with the carbon atom to which they are attached = C=O, L = CH₂CH₃, W is N(CH₃)₂, Z = OH and R₂' = Ac.

To a solution of the compound of Step 15f of Example 15 (700 mg, 0.8 mmol) in 10 ml of ethanol was added 25 ml of 1M HCl. The mixture was refluxed for 2 hours and then cooled to room temperature. The pH of the mixture was adjusted to pH=10 by addition of 2M NaOH and the mixture was extracted with ethyl acetate (25 ml x 3). The organic phases were
 5 dried over Na₂SO₄ and the solvent was removed *in vacuo*. The residue was purified by silica gel chromatography (hexanes:acetone / 1:1) to give the title compound (480 mg).

MS (ESI) m/z: 670.23 (M+H)⁺.

¹³C-NMR(100 MHz, CDCl₃): δ 216.3, 175.0, 170.1, 141.8, 122.1, 99.4, 81.1, 79.0, 77.7, 77.5, 76.2, 75.6, 72.1, 71.7, 68.8, 65.6, 63.2, 60.5, 46.5, 43.7, 40.8, 39.1, 38.6, 35.9, 31.1,
 10 23.0, 21.6, 21.3, 21.2, 19.8, 18.5, 17.3, 14.8, 14.3, 13.0, 11.7, 7.9.

Step 18b. Compound of formula I: A and B taken together with the carbon atom to which they are attached = C=CH₂, X and Y taken together with the carbon atom to which they are attached = C=O, L = CH₂CH₃, W is N(CH₃)₂, Z = OH and R₂' = H.

The title compound is prepared by refluxing the compound from Step 18a in methanol
 15 according to the procedure described in Example 1 (Step 1c).

Example 19

Compound of formula IV: A and B taken together with the carbon atom to which they are attached = C=CH₂-phenyl, Q = OH, R₂' = H, and R₄'' = Ac.

20 Step 19a: t-BuOC(O)OCH₂C(O)CH₂OC(O)OtBu

To a solution of 1,3-dihydroxyacetone dimer (36.03 g, 0.20 mol) and DMAP (1.22 g, 10.0 mmol) in dichloromethane (80 mL) and pyridine (97.0 mL, 1.20 mol) was added a solution of di-*tert*-butyl dicarbonate (200.0 g, 0.92 mol) in dichloromethane (40 mL) via a dropping funnel over 3 hours at room temperature. After stirring at room temperature for 15
 25 hours, the reaction mixture was condensed *in vacuo*. The residue was diluted with hexane:diethyl ether/1:1 and washed with saturated aqueous CuSO₄, water and brine. The organic phase was dried over Na₂SO₄ and the solvent was removed *in vacuo*. The residue was purified by silica gel chromatography (hexane:ethyl acetate/95:5~85:15) to give the title compound (45.0 g, 39% yield).

30 ¹³C-NMR (125 MHz, CDCl₃): δ 198.5, 152.6, 83.5, 68.5, 27.6.

Step 19b: Compound of formula 1-3 of Scheme 1: R = Phenyl and R₁₁ = *t*-Butyl.

A suspension of benzyltriphenylphosphonium bromide (520 mg, 1.20 mmol) in THF (5.0 mL) was treated with *n*-butyl lithium (1.6 M in hexane, 0.81 mL, 1.30 mmol) at -78 °C

under nitrogen with stirring. The mixture was warmed to -15°C over 1 hour before a solution of the compound from Step 19a (290 mg, 1.0 mmol) in THF (2.5 mL) was charged at -70°C . The reaction mixture was warmed to room temperature over 1 hour and left stirring for another 14 hours before partition (ethyl acetate and water). The organic phase was washed with water, brine and dried over Na_2SO_4 . The solvent was evaporated and the residue was purified by silica gel chromatography (hexane: CH_2Cl_2 /1:1) to give the title compound (253 mg, 70% yield).

^{13}C -NMR (125 MHz, CDCl_3): δ 153.1, 153.0, 135.1, 134.6, 130.4, 128.6, 128.2, 127.6, 82.0, 81.9, 68.4, 62.7, 27.6, 27.5.

10 Step 19c: Compound of formula IV: A and B taken together with the carbon atom to which they are attached = $\text{C}=\text{CH}_2$ -phenyl, $\text{Q} = \text{OAc}$, $\text{R}_2' = \text{Ac}$, and $\text{R}_4'' = \text{Ac}$.

A mixture of Erythromycin A oxime triacetate (525 mg, 0.60 mmol), the compound from Step 19b (250 mg, 0.69 mmol), 1,4-bis(diphenylphosphino)butane (51.2 mg, 0.12 mmol), and tris(dibenzylideneacetone)dipalladium (54.9 mg, 0.06 mmol) in THF (5.0 mL) was degassed and heated to and kept at 75°C for 15 hours before evaporation. The residue was purified by silica gel chromatography (hexane:acetone/4:1~1.5:1) to give the title compound as a 2.6:1 isomeric mixture (330 mg, 55% yield).

MS (ESI) m/z : 1003 ($\text{M}+\text{H}$) $^{+}$.

20 Step 19d: Compound of formula IV: A and B taken together with the carbon atom to which they are attached = $\text{C}=\text{CH}_2$ -phenyl, $\text{Q} = \text{OH}$, $\text{R}_2' = \text{H}$, and $\text{R}_4'' = \text{Ac}$.

The title compound was prepared by refluxing the compound from Step 19c in methanol according to the procedure described in Example 1 (Step 1c).

MS (ESI) m/z : 919 ($\text{M}+\text{H}$) $^{+}$.

25 Example 20

Compound of formula V: A and B taken together with the carbon atom to which they are attached are $\text{C}=\text{CH}$ -phenyl, $\text{Q} = \text{Ac}$, and $\text{R}_2' = \text{H}$.

Step 20a: Compound of formula V: A and B taken together with the carbon atom to which they are attached are $\text{C}=\text{CH}$ -phenyl, $\text{Q} = \text{H}$, and $\text{R}_2' = \text{Ac}$.

30 A solution of the compound of Example 19 (0.30 mmol) in methanol (5.0 mL) was treated with titanium(III) chloride (20% in 3% HCl , 0.77 mL) for 2 hours at room temperature then for 1 hour at 50°C before partition (CH_2Cl_2 and aqueous saturated NaHCO_3). The aqueous solution was extracted with CH_2Cl_2 . The combined extracts were

washed with brine and dried over Na_2SO_4 . After evaporation, the residue was purified by silica gel chromatography (CH_2Cl_2 :2 M NH_3 in MeOH/98:2–93:7) to give the title compound as a 4:1 isomeric mixture (105 mg, 50% yield).

MS (ESI) m/z : 703 ($\text{M}+\text{H}$)⁺.

5 Step 20b: Compound of formula V: A and B taken together with the carbon atom to which they are attached are $\text{C}=\text{CH}$ -phenyl, $\text{Q} = \text{Ac}$, and $\text{R}_2' = \text{Ac}$.

A solution of the compound from Step 20a (105 mg, 0.15 mmol) in CH_2Cl_2 (3.0 mL) was treated with triethylamine (104 μL , 0.74 mmol) and acetic anhydride (42 μL , 0.45 mmol) at room temperature for 19 hours before evaporation and drying in vacuo to give the title compound.

10 MS (ESI) m/z : 787 ($\text{M}+\text{H}$)⁺.

Step 20c. Compound of formula V: A and B taken together with the carbon atom to which they are attached are $\text{C}=\text{CH}$ -phenyl, $\text{Q} = \text{Ac}$, and $\text{R}_2' = \text{H}$.

The title compound is prepared by refluxing the compound from Step 20b in methanol according to the procedure described in Example 1 (Step 1c).

15

Example 21

Compound of formula I: A and B taken together with the carbon atom to which they are attached = $\text{C}=\text{O}$, X and Y taken together with the carbon atom to which they are attached = $\text{C}=\text{NAc}$, L = CH_2CH_3 , W is $\text{N}(\text{CH}_3)_2$, Z = $\text{OCH}_2\text{CH}=\text{CH}(\text{quinolin-3-yl})$, and $\text{R}_2' = \text{H}$.

20

Step 21a: Compound of formula I: A and B taken together with the carbon atom to which they are attached = $\text{C}=\text{O}$, X and Y taken together with the carbon atom to which they are attached = $\text{C}=\text{NH}$, L = CH_2CH_3 , W is $\text{N}(\text{CH}_3)_2$, Z = $\text{OCH}_2\text{CH}=\text{CH}(\text{quinolin-3-yl})$ and $\text{R}_2' = \text{H}$.

25 A solution of the title compound from Example 3 (0.5g, 0.8 mmol) in methanol (5 ml) and dichloromethane (5 ml) was cooled to -78°C and ozone was bubbled through the reaction until the solution became light blue. Then nitrogen was bubbled through the reaction mixture to remove excess ozone and triphenyl phosphine (1.0g, 3.8 mmol) was added. The solution was allowed to warm to room temperature over 1 hour. The solvent was evaporated and the residue was dissolved in 20 ml of THF and refluxed overnight. The solvent was removed under vacuum and the residue was purified by flash chromatography (SiO_2 , CH_2Cl_2 :2M ammonia in methanol = 95 : 5) to give the title compound (0.33g, 66%)

30

MS (ESI) m/z 629.2 ($\text{M}+\text{H}$)⁺

Step 21b. Compound of formula I: A and B taken together with the carbon atom to which they are attached = C=O, X and Y taken together with the carbon atom to which they are attached = C=NAc, L = CH₂CH₃, W is N(CH₃)₂, Z = OH and R₂' = Ac.

- 5 Acetic anhydride (0.17 ml, 1.5 mmol) was added to a solution of the compound from Step 21a (0.3 g, 0.5 mmol) and triethylamine (0.4 ml, 3.0 mmol) in dichloromethane (10 ml). The reaction mixture was stirred at room temperature for 4 hours, diluted with 100 ml of dichloromethane and washed with saturated sodium bicarbonate (3x100 ml) and brine (100 ml). The organic phase was dried over sodium sulfate and the solvent was removed *in vacuo*.
- 10 The residue was purified by silica gel chromatography (hexanes/acetone:1:1) to give the title compound (0.2 g).

MS (ESI) m/z: 713.1 (M+H)⁺.

- Step 21c. Compound of formula I: A and B taken together with the carbon atom to which they are attached = C=O, X and Y taken together with the carbon atom to which they are attached = C=NAc, L = CH₂CH₃, Z = OCH₂CH=CH(quinolin-3-yl) and R₂' = Ac.
- 15

- A mixture of the compound from Step 21b (55 mg, 0.08 mmol), 3-(*t*-butoxycarboxy)-3-(3-quinolinyl)-1-propene (60 mg, 0.21 mmol), and 1,4-bis(diphenylphosphino)-butane (10 mg, 0.02 mmol) was dissolved in freshly distilled THF (5.0 ml). To the solution was added
- 20 Pd₂(dba)₃ (12 mg, 0.01 mmol). The reaction mixture was heated to reflux slowly. After refluxing for 14 hours, the reaction was worked up as described in Step 1b of Example 1 and the solid residue was purified by silica gel chromatography (acetone : hexane/1:1) to give the title compound (27 mg).

MS (ESI) m/z 880.3 (M+H)⁺.

- 25 Step 21d: Compound of formula I: A and B taken together with the carbon atom to which they are attached = C=O, X and Y taken together with the carbon atom to which they are attached = C=NAc, L = CH₂CH₃, Z = OCH₂CH=CH(quinolin-3-yl) and R₂' = H.

- The title compound was prepared by refluxing the compound from Step 21c in
- 30 methanol according to the procedure described in Step 1c of Example 1.

MS (ESI) m/z 838.2 (M+H)⁺.

Selected ¹³C NMR: δ 206.0, 184.7, 176.2, 176.1, 149.1, 147.8, 133.0, 129.7, 129.6, 129.5, 128.2, 128.1, 127.8, 127.4, 101.1.

Example 22

Compound of formula I: A and B taken together with the carbon atom to which they are attached = C=CHCHCH-phenyl, X and Y taken together with the carbon atom to which they are attached = C=NAc, L = CH₂CH₃, W is N(CH₃)₂, Z = OC(O)-benzyl and R₂' = H.

Step 22a. Compound of formula I: A and B taken together with the carbon atom to which they are attached are C=CHCH=CH-phenyl, X and Y taken together with the carbon atom to which they are attached are C=NAc, L = CH₂CH₃, W is N(CH₃)₂, Z = OH, and R₂' = Ac.

To a solution of the compound of formula 1: A and B taken together with the carbon atom to which they are attached are C=CH₂, X and Y taken together with the carbon atom to which they are attached are C=NAc, L = CH₂CH₃, W is N(CH₃)₂, Z = OH, and R₂' = Ac (0.5 g, 0.7 mmol) in 8 ml anhydrous DMF, β -bromostyrene (0.15 ml, 1.2 mmol) and K₂CO₃ (200 mg, 1.5 mmol) were added at room temperature. The mixture was degassed briefly and a catalytic amount of dihydrogen dichlorobis(di-tert-butylphosphinito- κ P)palladate(II) (POPd from Combiphos catalysts, Inc.) was added. The reaction mixture was heated to 100°C in a sealed tube for 48 hours. Ethyl acetate (50 mL) was added and the solution was washed 3 times with aqueous NaHCO₃. The organic layer was dried over anhydrous Na₂SO₄. The solvent was evaporated under vacuum and the residue was purified by flash chromatography (SiO₂, acetone:hexanes/1:1) to provide the title compound.

MS (ESI) m/z 813 (M+H)⁺

Step 22b. Compound of formula I: A and B taken together with the carbon atom to which they are attached are C=CHCH=CH-phenyl, X and Y taken together with the carbon atom to which they are attached are C=NAc, L = CH₂CH₃, W is N(CH₃)₂, Z = OC(O)CH₂(2-pyridyl) and R₂' = Ac.

Into a solution of 2-pyridylacetic acid (85.4 mg, 0.48mmol) in CH₂Cl₂(1 ml) was added Et₃N (140 μ l) at room temperature. Then trimethyl acetic chloride (60 μ l, 0.48mmol) was added to the suspension at 0°C. After stirring at 0°C for 30 mins, a solution of the compound from Step 22b (100 mg, 0.12 mmol) in CH₂Cl₂(1 ml) in pyridine (100 μ l) was added at 0°C. The reaction mixture was warmed up to room temperature and stirred for overnight. The mixture was treated with saturated NaHCO₃, extracted with ethyl acetate and washed with brine. The organic phase was dried over sodium sulfate and the solvent was

removed *in vacuo*. The crude residue was purified by column chromatography (Aceton/Hexane 1:1) to give the title compound (83 mg).

MS (ESI) m/z : 932 (M+H)⁺.

5 Step 22c. Compound of formula I: A and B taken together with the carbon atom to which they are attached = C=CHCH=CH-phenyl, X and Y taken together with the carbon atom to which they are attached = C=NAc, L = CH₂CH₃, W is N(CH₃)₂, Z = OC(O)CH₂(2-pyridyl) and R₂' = H.

The title compound (71 mg) was prepared by stirring the compound from Step 22b in methanol overnight.

10 MS (ESI) m/z : 890 (M+H)⁺.

Example 23

Compound of formula I: Compound of formula I: A and B taken together with the carbon atom to which they are attached = C=CHCHCH-phenyl, X and Y taken together with the carbon atom to which they are attached = C=NAc, L = CH₂CH₃, W is N(CH₃)₂, Z =
15 OC(O)CH₂(3-pyridyl) and R₂' = H.

Step 23a. Compound of formula I: Compound of formula I: A and B taken together with the carbon atom to which they are attached = C=CHCH=CH-phenyl, X and Y taken together with the carbon atom to which they are attached = C=NAc, L =
20 CH₂CH₃, W is N(CH₃)₂, Z = OC(O)CH₂(3-pyridyl) and R₂' = Ac.

The title compound (59 mg) was prepared with the title compound from step 22a and 3-pyridylacetic acid according to the procedure described in Step 22 Step 1c).

MS (ESI) m/z : 932 (M+H)⁺.

Step 23c. Compound of formula I: A and B taken together with the carbon atom to which they are attached = C=CHCH=CH-phenyl, X and Y taken together with the carbon atom to which they are attached = C=NAc, L = CH₂CH₃, W is N(CH₃)₂, Z =
25 OC(O)CH₂(3-pyridyl) and R₂' = H

The title compound (52 mg) was prepared by stirring the compound from Step 23b in methanol for overnight.

30 MS (ESI) m/z : 890 (M+H)⁺.

Example 24

Compound of formula I: A and B taken together with the carbon atom to which they are attached = C=CH₂, X and Y taken together with the carbon atom to which they are attached = C=NOH, L = CH₂CH₃, W is N(CH₃)₂, Z = 4-oxocladinose and R₂' = H.

- 5 Step 24a. Compound of formula IV: A and B taken together with the carbon atom to which they are attached = C=CH₂, Q = OH, and R₂' = R₄'' = H.

Into a solution of the compound from Step 22b of example 22 (1g, 1.07 mmol) in 5 ml methanol was added LiOH(150 mg, 6.25 mmol) at rt. After stirring for overnight the mixture was diluted with ethyl acetate, and washed with saturated NH₄Cl and brine. The organic
10 phase was dried over Na₂SO₄, the solvent was removed *in vacuo* to give the title compound (0.9g).

MS (ESI) m/z: 800 (M+H)⁺.

Step 24b. Compound of formula IV: A and B taken together with the carbon atom to which they are attached = C=CH₂, Q = OAc, and R₂' = Ac, and R₄'' = H.

- 15 Into a solution of the compound from step 24a (1g, 1.25 mmol) in 2.5 ml CH₂Cl₂ was added Ac₂O (240 ul, 2.5 mmol) and DIEA(870 ul, 5 mmol) at room temperature. After stirring for 1 hour the mixture was diluted with ethyl acetate, and washed with saturated NaHCO₃ and brine. The organic phase was dried over Na₂SO₄, and the solvent removed *in vacuo* to give the crude title compound (1.2 g).

- 20 MS (ESI) m/z: 885 (M+H)⁺.

Step 24c. Compound of formula I: A and B taken together with the carbon atom to which they are attached = C=CH₂, X and Y taken together with the carbon atom to which they are attached = C=NOAc, L = CH₂CH₃, W is N(CH₃)₂, Z = 4-oxocladinose and R₂' = Ac.

- 25 Into a solution of the crude compound from step 24b in 7 ml of CH₂Cl₂ was added DMSO (1.3 ml, 18.75 mmol) and EDC-HCl (1.2 g, 6.25 mmol) at 0°C. Then Py-TFA (1.2 g, 6.25 mmol) was added at 0°C. The mixture was warmed to room temperature and stirred overnight. The mixture was diluted with ethyl acetate, and washed with saturated NaHCO₃ and brine. The organic phase was dried over Na₂SO₄, the solvent removed *in vacuo* and the
30 solid residue was purified by silica gel chromatography (acetone : hexane/1:1) to give the title compound (890 mg).

MS (ESI) m/z: 883 (M+H)⁺.

Step 24d. Compound of formula I: A and B taken together with the carbon atom to which they are attached = C=CH₂, X and Y taken together with the carbon atom to

which they are attached = C=NOH, L = CH₂CH₃, W is N(CH₃)₂, Z = 4-oxocladinose and R₂' = H.

A solution of the compound from Step 24c (50 mg) in 2 ml methanol was heated at 55°C for 48 hours. The solvent was removed *in vacuo* and the compound was purified by
5 column chromatography (CH₂Cl₂: 2M ammonia in MeOH/97:3) to give the title compound (20 mg).

MS (ESI) m/z: 799 (M+H)⁺.

Example 25

10 Compound of formula I: A and B taken together with the carbon atom to which they are attached = C=CH₂, X and Y taken together with the carbon atom to which they are attached = C=NOH, L = CH₂CH₃, W is N(CH₃)₂, Z = 4-oximecladinose and R₂' = H.

Into a solution of the compound from Step 24c of Example 24 (840 mg, 0.95 mmol) in 4 ml of 2-PrOH was added H₂NOH-HCl (140 mg, 1.9 mmol) at room temperature
15 followed by the addition of Et₃N (260 ul, 1.9 mmol). The mixture was stirred at room temperature for 2 hours and heated at 45°C for 20 minutes. Then acetic acid (108 ul) was added and the mixture heated at 40°C overnight. Another 70 mg of H₂NOH-HCl was added and the mixture heated at 45°C for 6 hours. The mixture was diluted with ethyl acetate, and washed with saturated NaHCO₃ and brine. The organic phase was dried over Na₂SO₄, the
20 solvent removed *in vacuo* and the solid residue was purified by silica gel chromatography (CH₂Cl₂: 2M ammonia in MeOH/97:3) to give the title compound (400 mg).
MS (ESI) m/z: 814 (M+H)⁺.

Example 26

25 Compound of formula IV: A and B taken together with the carbon atom to which they are attached are C=CH₂, Q = OH, and R₂' = R₄' = H.

A solution of the compound from Step 24b of example 24 (50 mg) in 2 ml methanol was heated at room temperature for 48 hours. The solvent was removed *in vacuo* and the compound was purified by column chromatography (CH₂Cl₂: 2M ammonia in MeOH/97:4)
30 to give the title compound (23 mg).
MS (ESI) m/z: 801 (M+H)⁺.

Example 27

Compound of formula I: Compound of formula IV: A and B taken together with the carbon atom to which they are attached = C=CH₂, Q = OH, R₂' = H, and R₄'' = Ac.

5 Step 27a. Compound of formula IV: A and B taken together with the carbon atom to which they are attached = C=CH₂, Q = OCH₃, R₂' = Ac, and R₄'' = Ac.

A mixture of the compound from Step 5a of Example 5 (100 mg, 0.11 mmol) and NaH (60% in mineral oil, 7 mg, 0.17 mmol) in 0.5 ml DMF was stirred at room temperature for one minute before methyl iodide (0.007 mL, 0.11 mmol) was added. After 15 minutes the mixture was quenched with water. The mixture was extracted with hexanes-ether (1:1). The
10 extracts were dried over Na₂SO₄ and the solvent was removed *in vacuo* to give the crude title compound (80 mg).

MS (ESI) m/z: 899 (M+H)⁺.

Step 27b. Compound of formula IV: A and B taken together with the carbon atom to which they are attached = C=CH₂, Q = OCH₃, R₂' = H, and R₄'' = H.

15 The title compound (40 mg) was prepared by stirring the compound from Step 27a (80 mg) in methanol at room temperature for 16 hours and refluxing for 2 hours according to the procedure described in Example 1 (Step 1c).

MS (ESI) m/z: 857 (M+H)⁺.

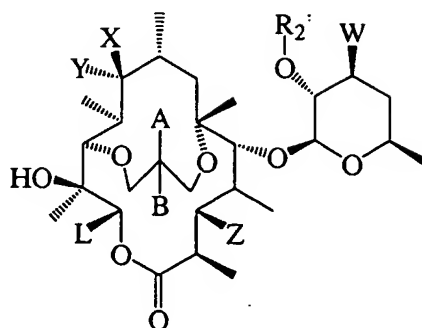
20 Although the invention has been described in detail with respect to various preferred embodiments it is not intended to be limited thereto, but rather those skilled in the art will recognize that variations and modifications may be made therein which are within the spirit of the invention and the scope of the appended claims.

25

WHAT IS CLAIMED IS:

1. A compound represented by the formula

5



(I)

10 as well as its pharmaceutically acceptable salts, esters and prodrugs,
wherein

A is selected from:

- a) -OH;
- b) -OR_p, where R_p is a hydroxy protecting group;
- 15 c) -R₁, where R₁ is independently selected from:
- (1) aryl;
 - (2) substituted aryl;
 - (3) heteroaryl; and
 - (4) substituted heteroaryl;
- 20 d) -OR₁, where R₁ is as previously defined;
- e) -R₂, where R₂ is selected from:
- (1) hydrogen;
 - (2) halogen;
 - (3) C₁-C₁₂ alkyl optionally containing 0, 1, 2, or 3 heteroatoms selected from O, S
- 25 or N, optionally substituted with one or more substituents selected from
halogen, aryl, substituted aryl, heteroaryl, and substituted heteroaryl;

- (4) C₂-C₁₂ alkenyl optionally containing 0, 1, 2, or 3 heteroatoms selected from O, S and N, optionally substituted with one or more substituents selected from halogen, aryl, substituted aryl, heteroaryl, and substituted heteroaryl; and
- (5) C₂-C₁₂ alkynyl optionally containing 0, 1, 2, or 3 heteroatoms selected from O, S and N, optionally substituted with one or more substituents selected from halogen, aryl, substituted aryl, heteroaryl, and substituted heteroaryl;
- f) -OR₂, where R₂ is independently previously defined;
- g) -S(O)_nR₁₁, where n = 0, 1 or 2, and R₁₁ is independently hydrogen, R₁ or R₂, where R₁ and R₂ are as previously defined;
- h) -NHC(O)R₁₁, where R₁₁ is as previously defined;
- i) -NHC(O)NHR₁₁, where R₁₁ is as previously defined;
- j) -NHS(O)₂R₁₁, where R₁₁ is as previously defined;
- k) NR₁₄R₁₅, where R₁₄ and R₁₅ are each independently R₁₁, where R₁₁ is as previously defined; and
- l) -NHR₃, where R₃ is an amino protecting group;

B is selected from:

- a) hydrogen;
- b) deuterium;
- c) halogen ;
- d) -OH;
- e) R₁, where R₁ is as previously defined;
- f) R₂, where R₂ is as previously defined; and
- g) -OR_p, where R_p is as previously defined, provided that when B is halogen, -OH, or -OR_p, A is R₁ or R₂;
- or alternatively, A and B taken together with the carbon atom to which they are attached are selected from:
- a) C=O;
- b) C(OR₂)₂, where R₂ is as previously defined;
- c) C(SR₂)₂, where R₂ is as previously defined;
- d) C(OR₁₂)(OR₁₃), where R₁₂ and R₁₃ are independently C₁-C₆ alkyl or taken together are -(CH₂)_m-, where m = 2 or 3;
- e) C(SR₁₂)(SR₁₃), where R₁₂, R₁₃, and m are as previously defined;
- f) C=CHR₁₁, where R₁₁ is as previously defined;

g) $C=N-O-R_{11}$, where R_{11} is as previously defined;

h) $C=N-O-Ar_1-M-Ar_2$, wherein

(1) $-Ar_1-$ is R_{31} , where R_{31} is independently selected from:

(a) $-R_1$, where R_1 is as previously defined;

(b) $-C_1-C_{12}$ alkyl optionally containing 0, 1, 2, or 3 heteroatoms selected from O, S or N, optionally substituted with one or more substituents selected from halogen, aryl, substituted aryl, heteroaryl, and substituted heteroaryl;

(c) $-C_2-C_{12}$ alkenyl optionally containing 0, 1, 2, or 3 heteroatoms selected from O, S and N, optionally substituted with one or more substituents selected from halogen, aryl, substituted aryl, heteroaryl, and substituted heteroaryl; or

(d) $-C_2-C_{12}$ alkynyl optionally containing 0, 1, 2, or 3 heteroatoms selected from O, S and N, optionally substituted with one or more substituents selected from halogen, aryl, substituted aryl, heteroaryl, and substituted heteroaryl;

(2) $-M-$ is absent or selected from:

(a) $-C_1-C_{12}$ alkyl optionally containing:

1. 0-3 heteroatoms selected from O, S or N; and
2. 0-3 groups selected from $-C=N-$, $-N=N-$ or $C(O)$;

(b) $-C_2-C_{12}$ alkenyl optionally containing:

1. 0-3 heteroatoms selected from O, S or N; and
2. 0-3 groups selected from $-C=N-$, $-N=N-$, or $C(O)$;

(c) $-C_2-C_{12}$ alkynyl optionally containing:

1. 0-3 heteroatoms selected from O, S or N; and
2. 0-3 groups selected from $-C=N-$, $-N=N-$, or $C(O)$;

(d) substituted aryl;

(e) substituted heteroaryl; or

(f) substituted heterocycloalkyl; and

(3) $-Ar_2$ is selected from:

(a) aryl;

(b) substituted aryl;

(c) heteroaryl; or

(d) substituted heteroaryl;

- i) $C=NNHR_{11}$, where R_{11} is as previously defined;
- j) $C=NNHC(O)R_{11}$, where R_{11} is as previously defined;
- k) $C=NNHC(O)NHR_{11}$, where R_{11} is as previously defined;
- l) $C=NNHS(O)_2R_{11}$, where R_{11} is as previously defined;
- 5 m) $C=NNHR_3$, where R_3 is as previously defined;
- p) $C=NR_{11}$, where R_{11} is as previously defined; or
- q) $C=N-N=CHR_{11}$, where R_{11} is as previously defined;

one of X and Y is hydrogen and the other is selected from:

- a) hydrogen;
- 10 b) deuterium;
- c) $-OH$;
- d) $-OR_p$, where R_p is as previously defined;
- e) $-NR_4R_5$, where R_4 and R_5 are each independently selected from:
 - (1) hydrogen;
 - 15 (2) C_1-C_{12} alkyl, optionally substituted with one or more substituents selected from halogen, aryl, substituted aryl, heteroaryl and substituted heteroaryl; or
 - (3) R_4 and R_5 , taken together with the nitrogen atom to which they are attached form a 3-10 membered heteroalkyl ring containing 0-2 additional hetero atoms selected from O, S and N; or

20 alternatively, X and Y taken together with the carbon atom to which they are attached are selected from:

- a) $C=O$;
- b) $C=N-Q$, wherein Q is selected from:
 - (1) R_{11} , where R_{11} is as previously defined;
 - 25 (2) amino protecting group;
 - (3) $C(O)R_{11}$, where R_{11} is as previously defined; or
 - (4) OR_6 , where R_6 is independently selected from:
 - (a) hydrogen;
 - (b) $-CH_2O(CH_2)_2OCH_3$,
 - 30 (c) $-CH_2O(CH_2O)_nCH_3$, where n is as previously defined;
 - (d) $-C_1-C_{12}$ alkyl, optionally substituted with one or more substituents selected from aryl, substituted aryl, heteroaryl and substituted heteroaryl;
 - (e) C_3-C_{12} cycloalkyl;

(f) C(O)-C₁-C₁₂ alkyl;

(g) C(O)-C₃-C₁₂ cycloalkyl;

(h) C(O)-R₁₁, where R₁₁ is as previously defined; or

(ii) -Si(R_a)(R_b)(R_c), wherein R_a, R_b and R_c are each independently selected

5 from C₁-C₁₂ alkyl, aryl and substituted aryl; or

(5) O-C(R₇)(R₈)-O-R₆, where R₆ is as previously defined, provided that R₆ is not

C(O)-C₁-C₁₂ alkyl, C(O)-C₃-C₁₂ cycloalkyl, or C(O)-R₁, and R₇ and R₈ taken

together with the carbon atom to which they are attached form a C₃-C₁₂

cycloalkyl group or each independently is selected from:

10 1. hydrogen; or

2. C₁-C₁₂ alkyl;

L is selected from:

b) -CH₃;

c) -CH₂CH₃;

15 d) -CH(OH)CH₃;

e) C₁-C₆ alkyl, optionally substituted with one or more substituents selected from aryl, substituted aryl, heteroaryl, and substituted heteroaryl;

f) C₂-C₆ alkenyl, optionally substituted with one or more substituents selected from aryl, substituted aryl, heteroaryl, and substituted heteroaryl; or

20 g) C₂-C₆ alkynyl, optionally substituted with one or more substituents selected from aryl, substituted aryl, heteroaryl, and substituted heteroaryl;

W is -NR₁₄R₁₅, where R₁₄ and R₁₅ are each independently selected from:

a) hydrogen;

25 b) C₁-C₁₂ alkyl, optionally substituted with one or more substituents selected from halogen, aryl, substituted aryl, heteroaryl and substituted heteroaryl;

c) C₁-C₁₂ alkenyl, optionally substituted with one or more substituents selected from halogen, aryl, substituted aryl, heteroaryl and substituted heteroaryl;

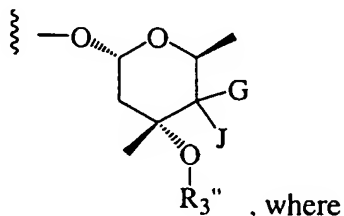
d) C₁-C₁₂ alkynyl, optionally substituted with one or more substituents selected from halogen, aryl, substituted aryl, heteroaryl and substituted heteroaryl; or

30 e) R₁₄ and R₁₅, taken together with the nitrogen atom to which they are attached form a heterocycloalkyl cyclic moiety;

Z is selected from:

(i) hydrogen;

- (j) $-\text{OH}$;
 (k) $-\text{OR}_p$, where R_p is as previously defined;
 (l) $-\text{OR}_{11}$, where R_{11} is as previously defined;
 (m) $-\text{OC}(\text{O})\text{R}_{11}$, where R_{11} is as previously defined;
 5 (n) $-\text{OC}(\text{O})\text{NHR}_{11}$, where R_{11} is as previously defined;
 (o) $-\text{S}(\text{O})_n\text{R}_{11}$, where n and R_{11} are as previously defined; or
 (p) -

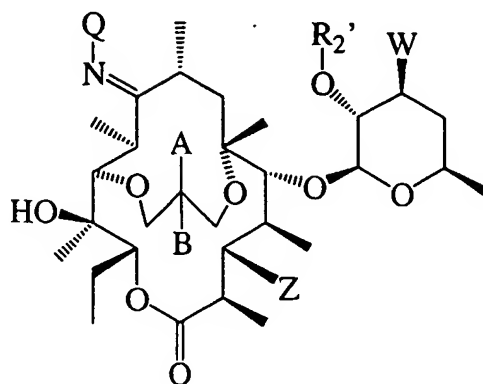


- i. R_3'' is hydrogen or methyl; and
 10 ii. where one of J or G is hydrogen, the other is selected from:
 1. hydrogen;
 2. deuterium;
 3. $-\text{OH}$;
 4. $-\text{OR}_p$, where R_p is previously defined;
 15 5. $-\text{OR}_4''$, where R_4'' is hydrogen or R_p , where R_p is as previously defined; or
 6. $-\text{NR}_4\text{R}_5$, where R_4 and R_5 is as previously defined; or
 iii. in the alternative, J and G are taken together with the carbon atom to which they are attached to form a group selected from:
 20 1. $\text{C}=\text{O}$;
 2. $\text{C}=\text{N}-\text{Q}$, wherein Q is as previously defined; and
 R_2' is hydrogen or R_p , where R_p is as previously defined.

25

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2. A compound according to claim 1, which is represented by formula II:

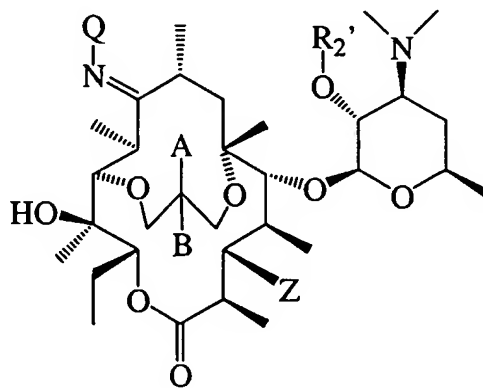


(II)

where A, B, Q, R₂', W, and Z are as previously defined.

5

3. A compound according to claim 1, which is represented by formula III:

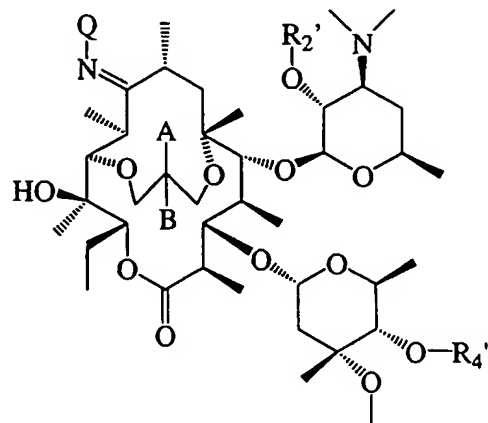


(III)

10

where A, B, Q, R₂', and Z are as previously defined.

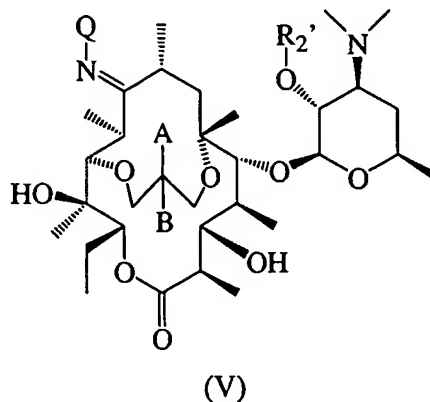
4. A compound according to claim 1, which is represented by formula IV:



(IV)

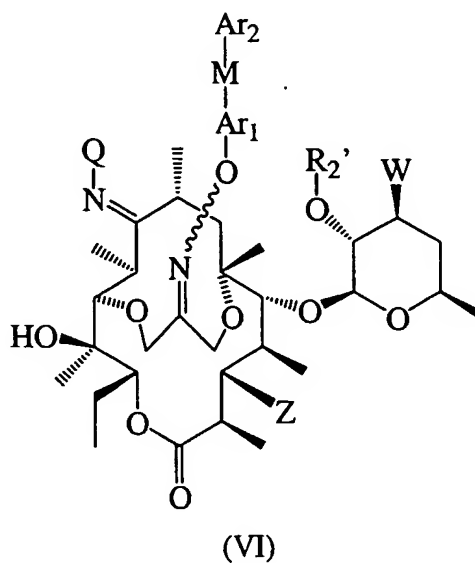
where A, B, Q, R₂', and R₄' are as previously defined.

5. A compound according to claim 1, which is represented by formula V:



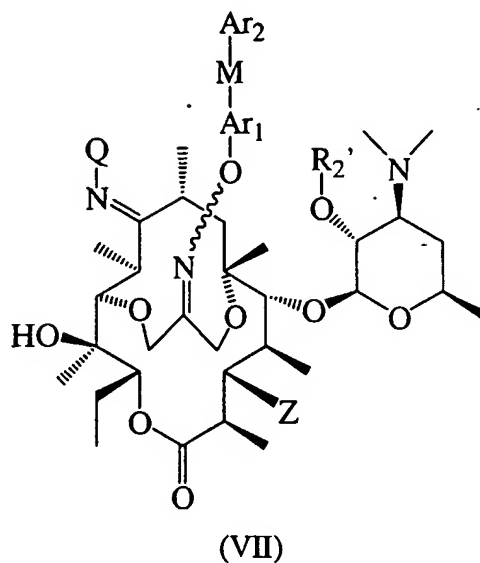
where A, B, Q, and R₂' are as previously defined.

6. A compound according to claim 1, which is represented by formula VI:



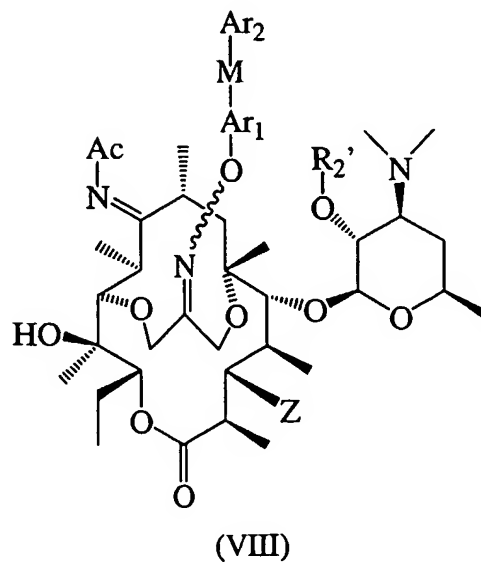
where Ar₁, Ar₂, M, Q, R₂', W, and Z are as previously defined.

7. A compound according to claim 1, which is represented by formula VII:



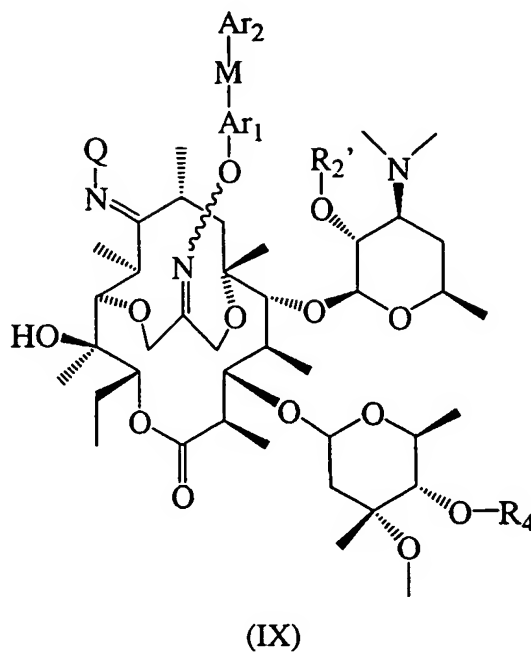
5 where Ar₁, Ar₂, M, Q, R₂', and Z are as previously defined.

8. A compound according to claim 1, which is represented by formula VIII:



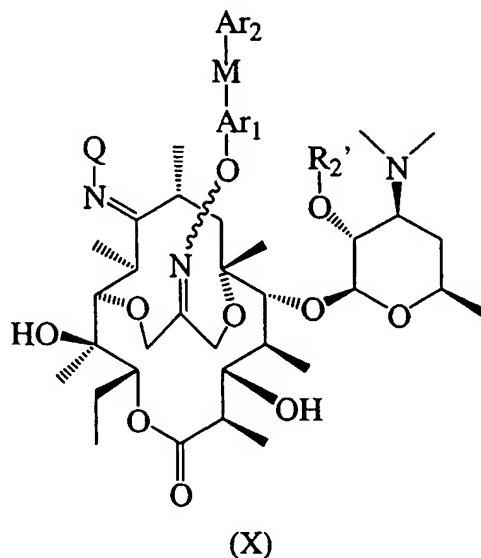
10 where Ar₁, Ar₂, M, R₂', and Z are as previously defined.

9. A compound according to claim 1, which is represented by formula IX:



5 where Ar₁, Ar₂, M, Q, R₂', and R₄' are as previously defined.

10. A compound according to claim 1, which is represented by formula X:



10

where Ar₁, Ar₂, M, Q, and R₂' are as previously defined.

11. A compound according to claim 1 which is selected from:

Compound of formula IV: A and B taken together with the carbon atom to which they are attached = C=CH₂, Q = OH, R₂' is H, and R₄' = Ac;

15

Compound of formula IV: A and B taken together with the carbon atom to which are attached = C=CH₂, Q = H, R₂' = H, and R₄'' = Ac;

Compound of formula V: A and B taken together with the carbon atom to which they are attached = C=CH₂, Q = H, and R₂' = H;

5 Compound of formula V: A and B taken together with the carbon atom to which they are attached = C=CH₂, Q = Ac, and R₂' = H;

Compound of formula IV: A and B taken together with the carbon atom to which they are attached = C=CH₂, Q = O-CH₂OCH₃, R₂' = H, and R₄'' = Ac;

10 Compound of formula V: A and B taken together with the carbon atom to which they are attached = C=CH₂, Q = O-CH₂OCH₃, and R₂' = H;

Compound of formula I: A and B taken together with the carbon atom to which they are attached = C=CH₂, X and Y taken together with the carbon atom to which they are attached = C=NAc, L = CH₂CH₃, W is N(CH₃)₂, Z = H and R₂' = H;

15 Compound of formula I: A and B taken together with the carbon atom to which they are attached = C=CH₂, X and Y taken together with the carbon atom to which they are attached = C=NAc, L = CH₂CH₃, Z = OC(O)(p-nitrophenyl) and R₂' = H;

Compound of formula I: A and B taken together with the carbon atom to which they are attached = C=CH₂, X and Y taken together with the carbon atom to which they are attached = C=NAc, L = CH₂CH₃, W is N(CH₃)₂, Z = OC(O)[2-(NO₂), 4-(CF₃)Phenyl] and R₂' = H;

20 Compound of formula I: A and B taken together with the carbon atom to which they are attached = C=CH₂, X and Y taken together with the carbon atom to which they are attached = C=NAc, L = CH₂CH₃, W is N(CH₃)₂, Z = OC(O)CH₂(p-methoxyphenyl) and R₂' = H;

25 Compound of formula IV: A and B taken together with the carbon atom to which they are attached = C=CH₂, Q = Ac, R₂' = H, and R₄'' = Ac;

Compound of formula I: Compound of formula IV: A and B taken together with the carbon atom to which they are attached = C=O, Q = Ac, R₂' = H, and R₄'' = Ac;

30 Compound of formula IV: A and B taken together with the carbon atom to which they are attached = C=OBz, Q = Ac, R₂' = H, and R₄'' = Ac;

Compound of formula IV: A and B taken together with the carbon atom to which they are attached = C=(3-quinolyl), Q = Ac, R₂' = H, and R₄'' = Ac;

- Compound of formula I: A and B taken together with the carbon atom to which they are attached = C=CH₂, X and Y taken together with the carbon atom to which they are attached = C=O, L = CH₂CH₃, W is N(CH₃)₂, Z = 4-acetoxycladinoside and R₂' = H;
- 5 Compound of formula I: A and B taken together with the carbon atom to which they are attached = C=CH-quinolin-3-yl, X and Y taken together with the carbon atom to which they are attached = C=O, L = CH₂CH₃, W is N(CH₃)₂, Z = 4-acetoxycladinoside and R₂' = H;
- 10 Compound of formula I: A and B taken together with the carbon atom to which they are attached = C=CH-quinolin-3-yl, X and Y taken together with the carbon atom to which they are attached = C=O, L = CH₂CH₃, W is N(CH₃)₂, Z = OH, and R₂' = H;
- Compound of formula I: A and B taken together with the carbon atom to which they are attached = C=CH₂, X and Y taken together with the carbon atom to which they are attached = C=O, L = CH₂CH₃, W is N(CH₃)₂, Z = OH and R₂' = H;
- 15 Compound of formula IV: A and B taken together with the carbon atom to which they are attached = C=CH₂-phenyl, Q = OH, R₂' = H, and R₄'' = Ac;
- Compound of formula V: A and B taken together with the carbon atom to which they are attached are C=CH-phenyl, Q = Ac, and R₂' = H;
- Compound of formula I: A and B taken together with the carbon atom to which they are attached = C=O, X and Y taken together with the carbon atom to which they are attached = C=NAc, L = CH₂CH₃, W is N(CH₃)₂, Z = OCH₂CH=CH(quinolin-3-yl), and R₂' = H;
- 20 Compound of formula I: A and B taken together with the carbon atom to which they are attached = C=CHCHCH-phenyl, X and Y taken together with the carbon atom to which they are attached = C=NAc, L = CH₂CH₃, W is N(CH₃)₂, Z = OC(O)-benzyl and R₂' = H;
- 25 Compound of formula I: A and B taken together with the carbon atom to which they are attached = C=CHCHCH-phenyl, X and Y taken together with the carbon atom to which they are attached = C=NAc, L = CH₂CH₃, W is N(CH₃)₂, Z = OC(O)CH₂(2-pyridyl) and R₂' = H;
- 30 Compound of formula I: A and B taken together with the carbon atom to which they are attached = C=CH₂, X and Y taken together with the carbon atom to which they are attached = C=NOH, L = CH₂CH₃, W is N(CH₃)₂, Z = 4-oxocladoside and R₂' = H;

Compound of formula I: A and B taken together with the carbon atom to which they are attached = C=CH₂, X and Y taken together with the carbon atom to which they are attached = C=NOH, L = CH₂CH₃, W is N(CH₃)₂, Z = 4-oximecladinose and R₂' = H;

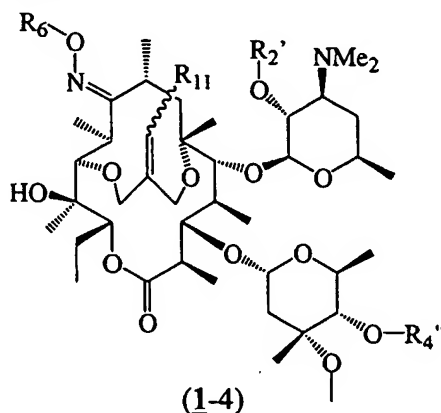
Compound of formula IV: A and B taken together with the carbon atom to which they are attached are C=CH₂, Q = OH, and R₂' = R₄'' = H; or

Compound of formula I: Compound of formula IV: A and B taken together with the carbon atom to which they are attached = C=CH₂, Q = OH, R₂' = H, and R₄'' = Ac.

12. A pharmaceutical composition comprising a therapeutically effective amount of a compound of claim 1, or its pharmaceutically-acceptable salt, ester or prodrug, in combination with a pharmaceutically acceptable carrier.

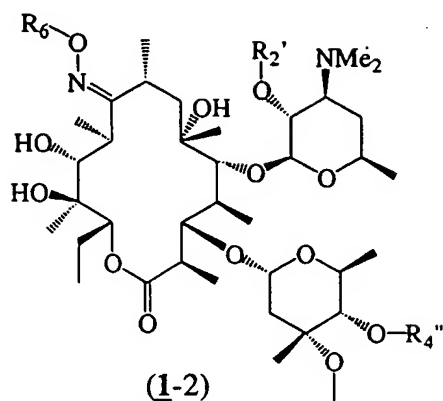
13. A method for controlling a bacterial infection in a subject in need of such treatment, comprising administering to said subject a therapeutically effective amount of a pharmaceutical composition according to claim 12.

14. A process for preparing a compound according to the formula



wherein R₆, R₁₁, R₂' and R₄'' are as defined in claim 1 comprising:

20 (a) reacting a compound represented by the formula



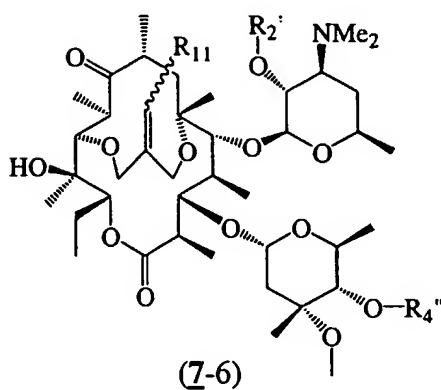
, wherein R_6 , R_2' and R_4'' are as defined in claim 1,

with an alkylating agent represented by the formula:

$R_{12}-OC(O)O-CH_2[C=CHR_{11}]CH_2-OC(O)-OR_{12}$ (1-3), wherein R_{12} is $C_1 - C_6$ - alkyl and R_{11} is as defined in claim 1, in an aprotic solvent in the presence of a palladium catalyst at a temperature of from room temperature to about 80°C .

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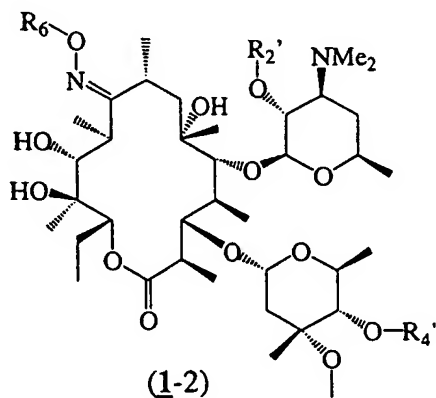
15. A process for preparing a compound represented by the formula:



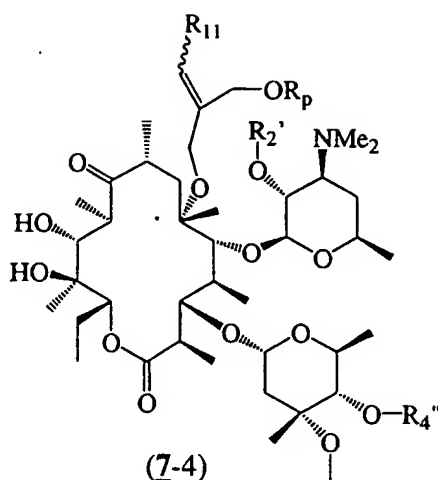
, wherein R_{11} , R_2' and R_4'' are as defined in claim 1,

10 comprising:

(a) reacting a compound represented by the formula

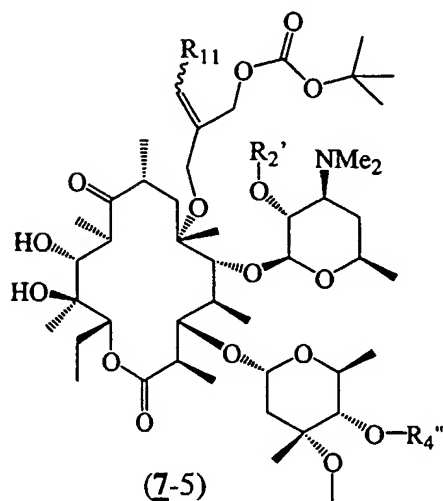


wherein R_6 is as defined in claim 1 and R_2' and R_4'' are as previously defined,



wherein R_{11} , R_2' , R_4'' and R_p are as previously defined;

(d) reacting the compound from (c) to provide a compound represented by the formula



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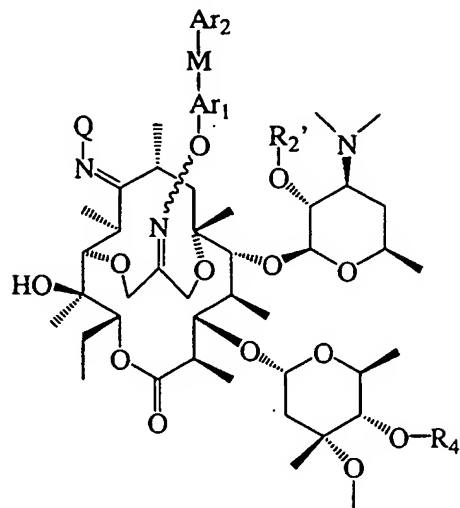
, wherein R_{11} , R_2' and R_4'' are as previously defined; and

(e) cyclizing the compound from (d) with a palladium catalyst in an aprotic solvent at from room temperature to about 80°C.

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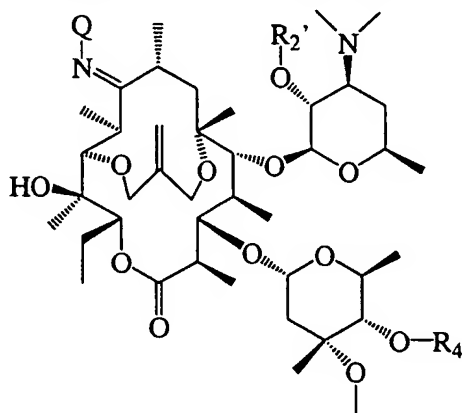
16. A process for the preparation of a compound represented by the formula (IX):



(IX), where Q , Ar_1 , M , Ar_2 and R_2' are as defined

in claim 1, comprising the steps of:

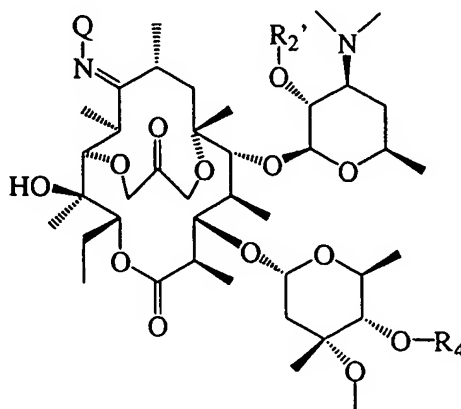
(a) reacting a compound represented by the formula (16a)



(16a), where Q , R_2' , and R_4 are as

previously defined, with a reagent or reagents capable of performing oxidative cleavage;

(b) reacting a compound from step (a) represented by the formula (16b)



(16b), where Q , R_2' , and R_4 are as

previously defined, with a compound of the formula

$\text{Ar}_1\text{-M-Ar}_2\text{-O-NH}_2$, wherein Ar_1 , Ar_2 , and M are defined as in claim 1, in the presence of an acid or a base; and

(c) optionally deprotecting the compound from step (d).

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07H17/00 A61K31/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07H A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 6 046 171 A (LI LEPING ET AL) 4 April 2000 (2000-04-04) the whole document ---	1-16
A	WO 99 21864 A (ABBOTT LAB) 6 May 1999 (1999-05-06) the whole document -----	1-16



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Patent family members are listed in annex.

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Date of the actual completion of the international search

21 July 2003

Date of mailing of the international search report

30/07/2003

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Koessler, J-L

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Application No

PCT/US 03/14914

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